Chemoenzymatic Formation of Biologically Relevant Nitrogen Heterocycles

Een wetenschappelijke proeve op het gebied van de
Natuurwetenschappen, Wiskunde en Informatica

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"Life is not measured by the number of breaths we take – but by the moments that take our breath away"

Hilary Cooper

"A good gulp of hot whiskey at bedtime – it's not very scientific but it helps"

Alexander Fleming

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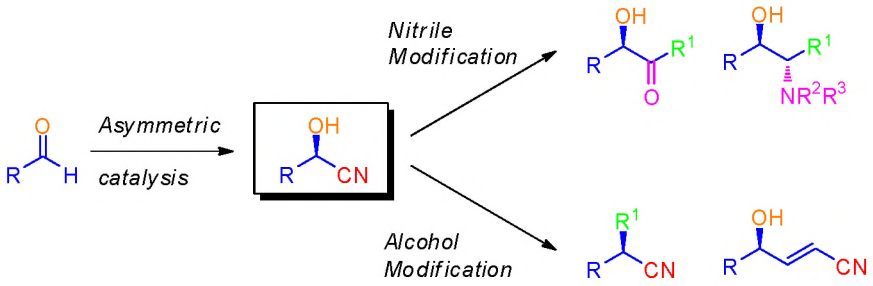
List of Abbreviations

[α]	Specific rotation
Ac	acetyl
ACN	2,2'-azocyclohexanecarbonitrile
AIBN	2,2'-azobisisobutyronitrile
ATR	attenuated total reflexion
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bs	broad singlet (NMR)
^{t}Bu	*tert*-butyl
c	concentration (g/100 mL)
°C	degrees Celcius (centigrade)
calcd	calculated
cat	catalytic/catalyst
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CI	chemical ionization
d (NMR)	doublet
δ	chemical shift
Δ	reflux
DBU	1,8-diazabicyclo[5,4,0]undec-7-een
dd (NMR)	doublet of doublets
DIBALH	diisobutylaluminium hydride
DIPE	diisopropylether
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	diphenylphosphinoferrocene
dr	diastereomeric ratio
dt (NMR)	doublet of triplets
ee	enantiomeric excess
e.g.	*exempli gratia* (for example)
EI	electron impact
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
et al.	*et aliae* (and others)
Et_3N	triethylamine
Fmoc	9-fluorenylmethoxycarbonyl
g	gram
GC	gas chromatography
h	hours
HNL	hydroxylnitrile lyase
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	*iso*-
i.e.	*id est* (that is)
Im	imidazole
$(Im)_2CO$	1,1'-carbonyldiimidazole
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide
m	milli
m (NMR)	multiplet
M	molar
Me	methyl
MeCN	acetonitrile
min	minutes
MIP	2-methoxy *iso*-propyl
Mp	melting point
NMR	nuclear magnetic resonance
PCC	pyridinium chloroformate
PG	protecting group
ppm	parts per million
py	pyridine
q (NMR)	quartet
quant	quantitative
R_f	retention factor
rt	room temperature
s (NMR)	singlet
s.m.	starting material
t (NMR)	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl, 4-toluenesulfonyl

Chapter 1

Synthetic Applications of Enantiopure Cyanohydrins



Cyanohydrins are synthetically versatile building blocks and can be readily elaborated into a large variety of molecules, which are of relevance for the fields of organic chemistry, medicinal chemistry, and materials science. This chapter provides an overview of the synthetic applications of enantiomerically pure cyanohydrin building blocks that have been reported in recent years.

Part of this chapter will be published in: Ritzen, B.; van Delft, F. L.; Rutjes, F. P. J. T. Synthetic Applications of Enantiopure Cyanohydrins, *manuscript in preparation.*

1.1 Introduction

Since the discovery of the enantioselective enzyme-catalyzed addition of hydrogen cyanide to aldehydes by Rosentaler in 1908,[1] non-racemic cyanohydrins and their derivatives have gained considerable interest as valuable building blocks for the synthesis of enantiomerically pure compounds. Consequently, various methods for cyanohydrin synthesis have been reported including metal catalysis, organocatalysis, and enzyme catalysis, and have been comprehensively covered in several reviews.[2] In turn, these cyanohydrins have been extensively used as key building blocks for synthesizing more complex structures and as a result have found widespread application in all fields of chemistry. Not only the hydroxyl and nitrile groups can be modified, but also the cyanohydrin side chain(s) can be altered to further enrich the follow-up chemistry. In contrast to the increasing importance as a privileged reactive functionality, there has not been any recent comprehensive coverage of the synthetic applications of this compound class.[2b,d,e] Hence, this chapter summarizes the recent advances in synthetic applications of cyanohydrins in organic chemistry covering the literature from 2003 to 2010. Thereby we have restricted ourselves to synthetic applications starting from enantiomerically pure cyanohydrins generated through any form of asymmetric catalysis.

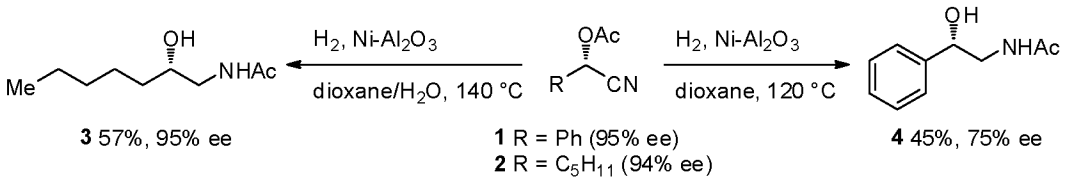
1.2 Modification of the nitrile group

1.2.1 Nitrile reduction

1.2.1.1 Synthesis of amino alcohols

Catalytic hydrogenation of optically active cyanohydrin esters proved to be a viable strategy for the synthesis of pharmaceutically relevant *N*-acetylated-β-amino alcohols. Hanefeld *et al.* used a catalyst-solvent combination of nickel on alumina in dioxane for the hydrogenation of acylated cyanohydrins **1** and **2** (Scheme 1.1).[3] Subsequent intramolecular acetyl migration smoothly furnished the desired products in fair to good yields for aliphatic substrates (*e.g.* **3**) and acceptable yields for more sensitive benzylic substrates such as **4**. In case of the optically active benzylic cyanohydrin **1**, a decrease in ee was observed due to the sensitivity of the benzylic proton under the reaction conditions, while for the aliphatic substrate **2** the optical activity remained unchanged.

Scheme 1.1 *Nitrile reduction and intramolecular acetyl transfer.*



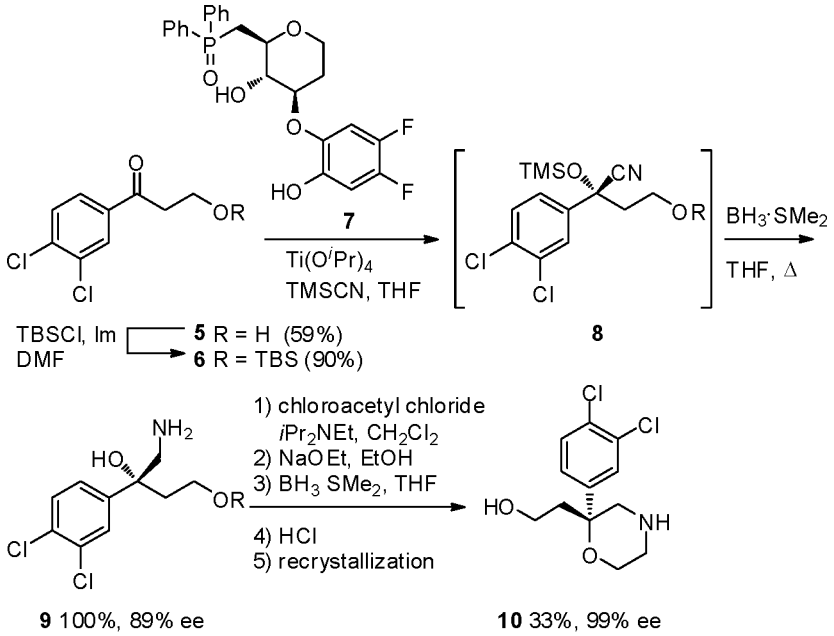
3 57%, 95% ee

1 R = Ph (95% ee)
2 R = C_5H_{11} (94% ee)

4 45%, 75% ee

The Shibasaki group developed an elegant method for the synthesis of the morpholine-based intermediate **10** of neurokinin receptor antagonists by use of the asymmetric bifunctional catalyst **7** (Scheme 1.2).[4] The sequence commenced with the formation of ketone **6**, which served as a building block in the key catalytic asymmetric cyanosilylation reaction. This cyanosilylation provided the unstable cyanohydrin **8**, which was directly reduced by borane giving rise to amino alcohol **9** in an enantioselective manner. Condensation with chloroacetyl chloride, ring closure under basic conditions, reduction and deprotection furnished the key morpholine **10** in excellent enantiopurity after recrystallization.

Scheme 1.2 *Asymmetric synthesis of a morpholine–based neurokinin receptor antagonist.*



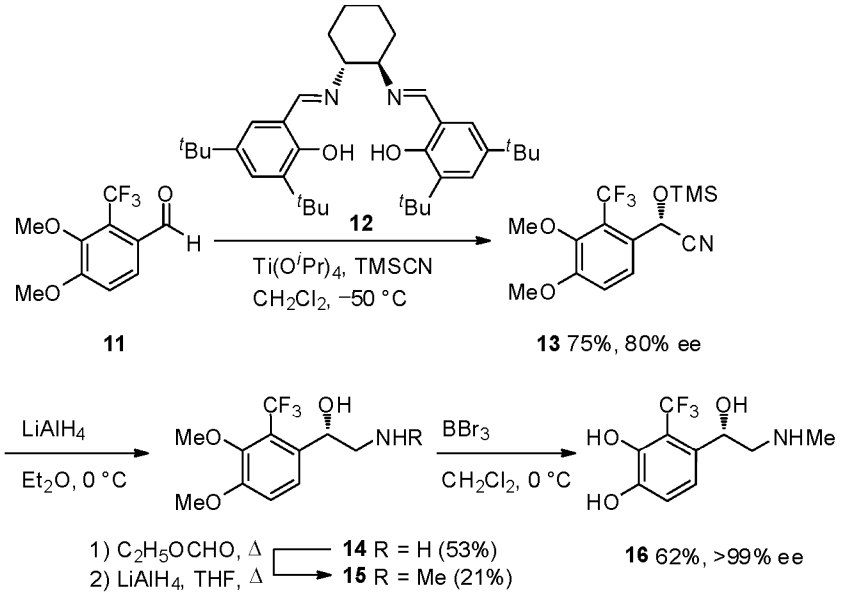
9 100%, 89% ee

10 33%, 99% ee

Ammann *et al.* explored an asymmetric route to trifluoromethyl-analogues of epinephrine.[5] In this strategy, the formation of the enantioenriched cyanohydrin building block **13** was accomplished by reacting veratraldehyde derivative **11** with TMSCN in the presence of the

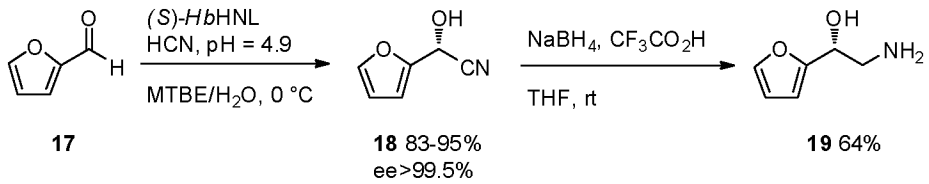
chiral (*R*,*R*)-salen ligand **12** and a titanium source (Scheme 1.3). Treatment with $LiAlH_4$, followed by monomethylation using ethyl formate and reduction yielded after recrystallization (*S*)-trifluoromethylepinephrine precursor **15**. De-*O*-methylation of the latter compound finally led to the formation of the target molecule **16** in 62% yield.

Scheme 1.3 *Asymmetric synthesis of trifluoromethylepinephrines.*



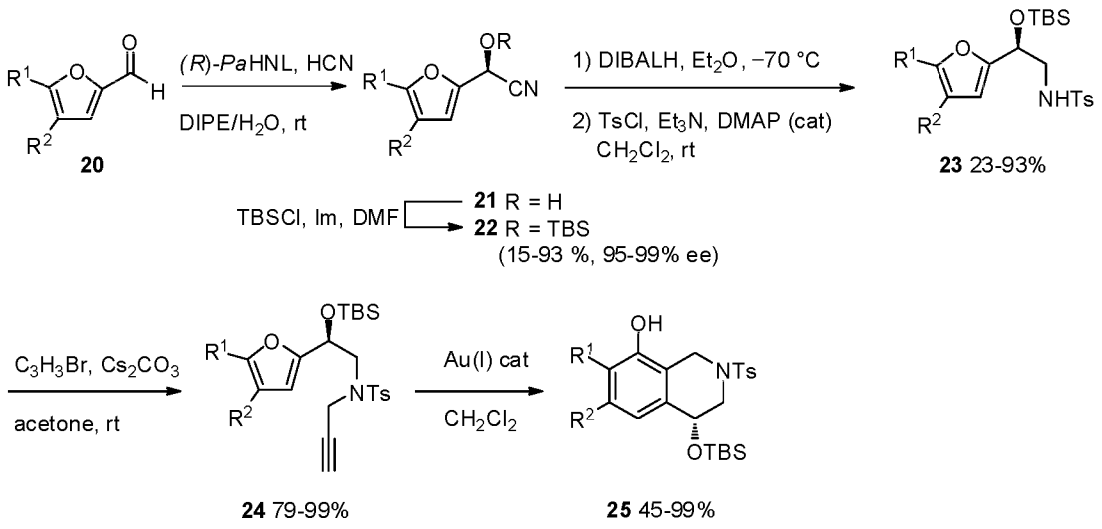
In 2006, researchers at DSM (Geleen, the Netherlands) developed a two-step industrially scalable chemoenzymatic route to (*R*)-2-amino-1-(2-furyl)ethanol (**19**) *via* reduction of cyanohydrins, which in principle, could also be attractive for the synthesis of a large array of amino alcohols bearing a primary amine functionality (Scheme 1.4).[6] Thus, the generation of enantiopure cyanohydrin **18** was accomplished by subjection of furfural (**17**) to an enzyme-catalyzed hydrocyanation by recombinant HNL from *Hevea brasiliensis*. Reduction of the crude cyanohydrin **18** to yield the vicinal amino alcohol **19** in 64% yield and excellent ee was conveniently accomplished with $NaBH_4$.

Scheme 1.4 *Large scale chemoenzymatic synthesis of* ***19****.*



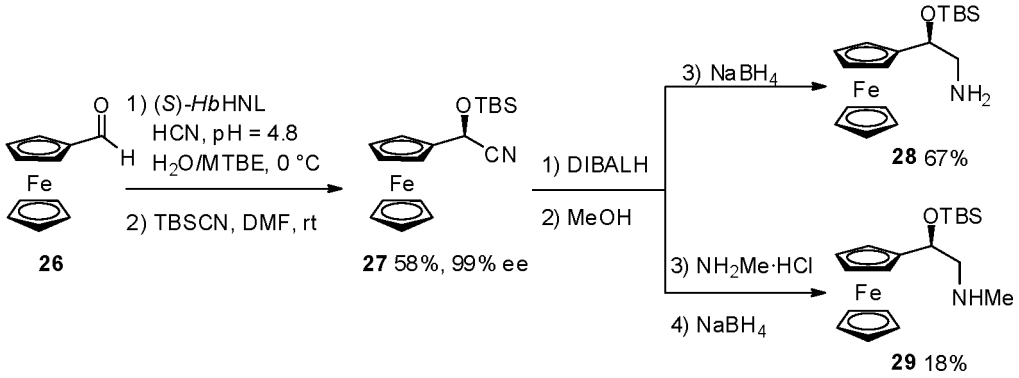
Recently, Hashmi *et al.* converted a series of five furfural derivatives with various substitution patterns to the corresponding protected enantiopure cyanohydrins **22** using the (*R*)-selective *Pa*HNL enzyme (Scheme 1.5).[7] After a sequence of standard operations, including DIBALH reduction, followed by tosylation to sulfonamide **23** and propargylation, precursors **24** were obtained. Subsequent treatment of the alkynyl functionalized furans **24** in a gold(I)-catalyzed cycloisomerization delivered the dihydroxytetrahydroisoquinolines **25** in good yield and high enantiomeric purity.

Scheme 1.5 *Enantioselective chemoenzymatic synthesis of tetrahydroisoquinolines.*



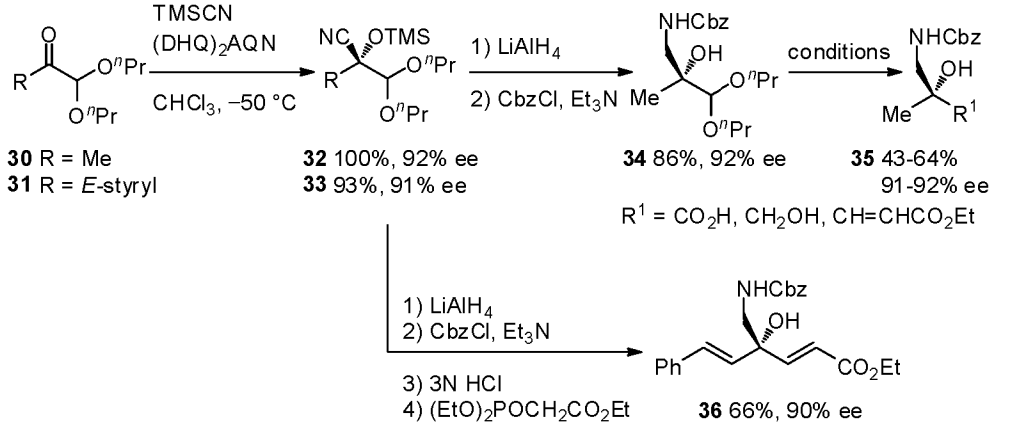
Griengl *et al.* developed novel chiral ferrocene-based cyanohydrins *via* stereoselective (*S*)-*Hb*HNL-catalyzed hydrogen cyanide addition onto formylferrocenes **26**.[8] As shown in Scheme 1.6, the corresponding cyanohydrin **27** was obtained in excellent enantioselectivity and an acceptable 58% yield. Further transformation of the nitrile functionality by means of different reductive pathways provided direct access to amino alcohols **28** and **29** which are useful precursors for *e.g.* inter- and intramolecularly linked ferrocene analogues,[9] and ferrocenyl-oxazolidinone-based chiral auxiliaries.[10]

Scheme 1.6 *Chemoenzymatic synthesis of chiral ferrocene derivatives.*



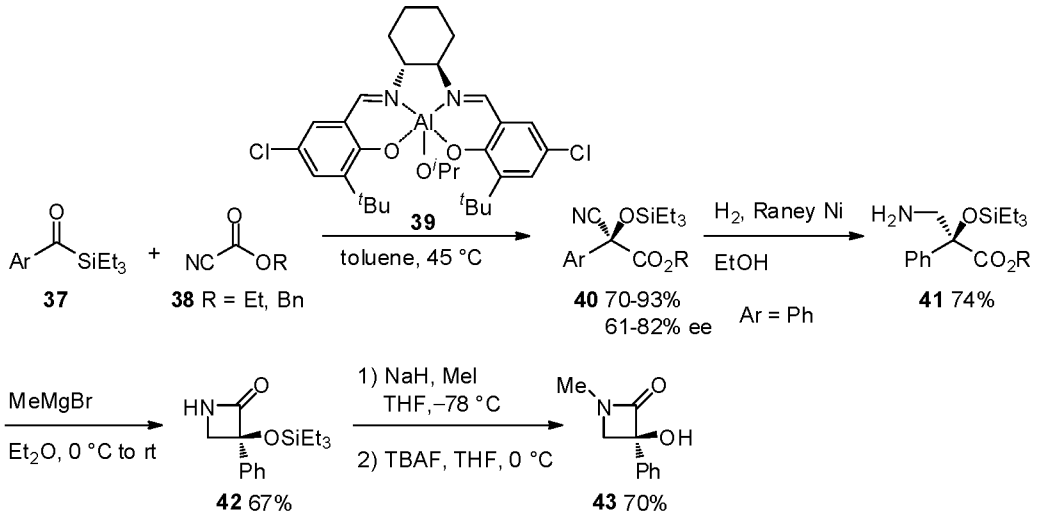
Catalytic asymmetric cyanation of prochiral ketones provides a useful method for the preparation of chiral building blocks bearing a quaternary center. Well aware of their importance as functional synthons in organic synthesis together with the use of cinchona alkaloids as well-known organocatalysts, the group of Deng described an asymmetric cyanosilylation of acetal ketones **30** and **31** catalyzed by readily available cinchona alkaloids.[11] This cyanosilylation was applied to the synthesis of several optically active multifunctional chiral building blocks as depicted in Scheme 1.7. Analogously, a similar method was used to generate chiral tertiary cyanohydrin carbonates. In this case ethyl cyanoformate instead of TMSCN was used in the catalytic step.[12] The authors also demonstrated that these compounds could be successfully converted into chiral β-amino alcohols and α-hydroxy acids.

Scheme 1.7 *Catalytic asymmetric synthesis of amino alcohols.*



A new catalytic asymmetric cyanation–1,2-Brook rearrangement–*C*-acylation reaction of acylsilanes **37** with chloroformates **38** was studied by Johnson and co-workers.[13] The cyano ester products **40** of the reaction sequence were obtained in high yield and good levels of stereocontrol by invoking Jacobsen's (salen)aluminum complex **39** (Scheme 1.8). Moreover, these compounds could serve as building blocks for further functional group modification as shown for the synthesis of **41** by chemoselective nitrile reduction followed by cyclization into lactam **43**.[14]

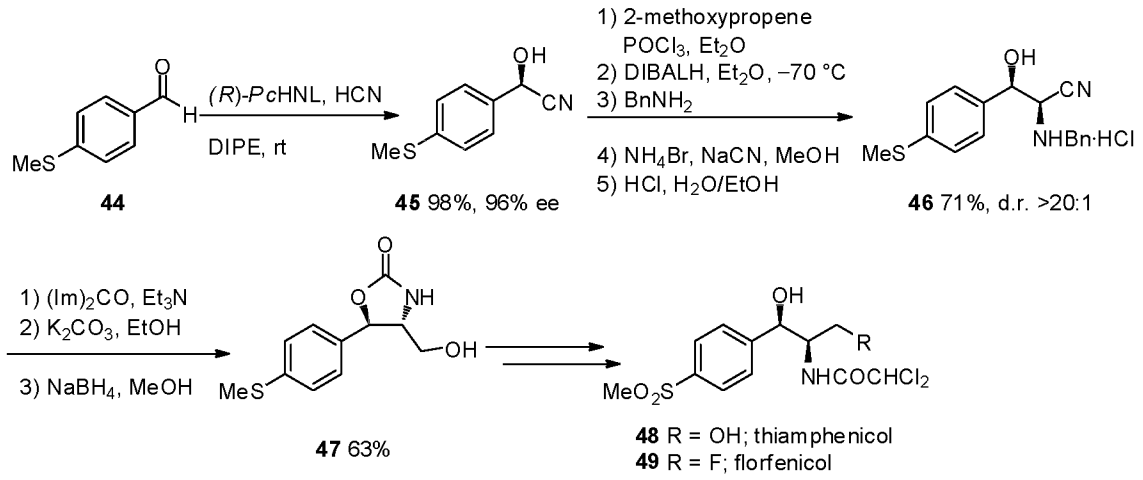
Scheme 1.8 *Enantioselective catalytic acylation of (silyloxy)nitrile anions and nitrile reduction.*



1.2.1.2 Applications in transimination reactions

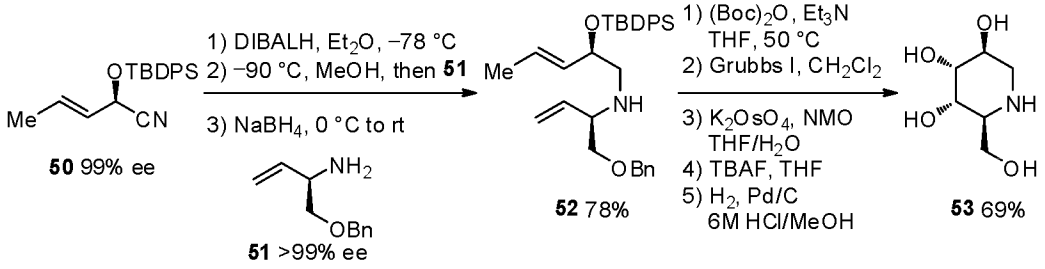
4-(Methylthio)benzaldehyde **44** served for Lu and co-workers as a starting material for the preparation of the antibiotics thiamphenicol (**48**) and florfenicol (**49**) (Scheme 1.9).[15] They found that the hydroxynitrile lyase (HNL) *Prunus communis* L. var. *dulcis*, isolated from the kernel of *Badamu* almonds, stereoselectively produced the corresponding (*R*)-cyanohydrin **45** in 98% yield and 96% ee, which after recrystallization resulted in pure **45**. A one-pot reaction sequence including DIBALH reduction of the MIP-protected cyanohydrin, followed by benzylamine addition, and a diastereoselective Strecker reaction provided the second stereocenter (dr >20:1). Next, transformation of the resulting aminonitrile **46** *via* three standard operations gave oxazolidinone **47**, which was the key intermediate in the synthesis of thiamphenicol (**48**) and florfenicol (**49**).

Scheme 1.9 *Asymmetric synthesis of thiamphenicol (48) and florfenicol (49).*



Overkleeft *et al.* reported a novel chemoenzymatic approach of three 1-deoxynojirimycin (DNJ) iminosugar derivatives.[16] The key step involved application of the silyl-protected cyanohydrin **50** in an efficient one-step DIBALH reduction–transimination–reduction sequence. Boc-protection in heated THF and RCM with the first generation Grubbs catalyst delivered the cyclic iminosugar precursor skeleton (Scheme 1.10). Next, application of the Upjohn dihydroxylation on the latter compound smoothly generated the hydroxylated piperidine as a single enantiomer which after deprotection was converted into L-*altro*-1-DNJ (**53**) in 69% overall yield from **52**. In a similar fashion, the authors successfully applied the methodology for the synthesis of D-*allo*-1-DNJ and D-*galacto*-1-DNJ using *ent*-**51**.

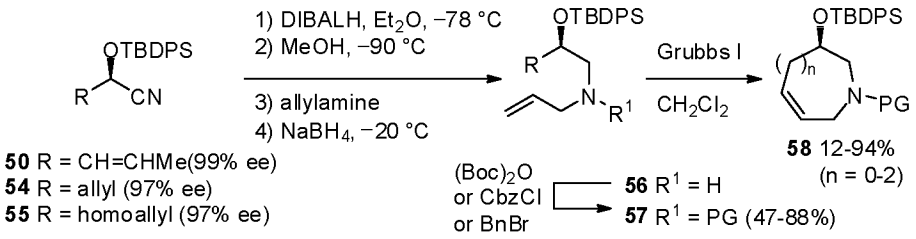
Scheme 1.10 *Chemoenzymatic synthesis of L-altro-1-DNJ (53).*



The group of van der Gen showed that cyanohydrins are valuable building blocks for the construction of different nitrogen heterocycles (Scheme 1.11).[17] *Via* an elegant one-pot DIBALH reduction–transimination–$NaBH_4$-reduction sequence, the cyanohydrins **50**, **54** and

55 were transformed into the secondary amines **56** and protected with a suitable protection group *i.e.* Boc, Cbz or Bn, delivering products **57** in good yields (47-88%). Finally, ring-closing metathesis with the Grubbs-I catalyst led to the desired ring systems without loss of enantiopurity. Additionally, the investigators showed that *via* a similar approach cyclic unsaturated 1,2-ethanolamines could be prepared.

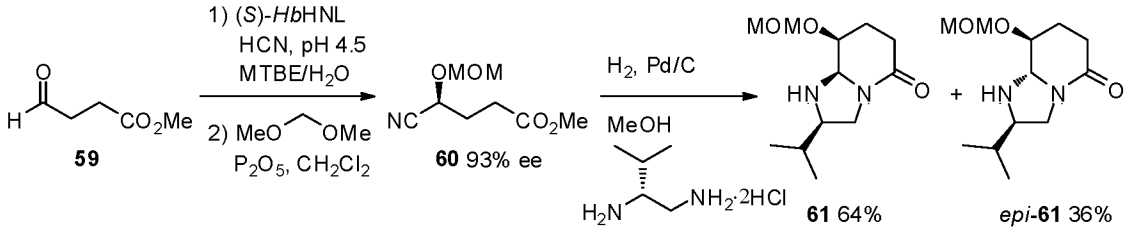
Scheme 1.11 *Synthesis of protected unsaturated carba- and nitrogen heterocycles.*



1.2.1.3 Applications in *N*-acyliminium ion chemistry

In a research program aiming at the synthesis of 5-hydroxypiperidone by partial reduction of enantiopure cyanohydrin **60**, Rutjes and coworkers came across a novel biocatalytic approach giving access to bicyclic *N,N*-acetals **61** in good yield (Scheme 1.12).[18] In this single-step process, partial reduction of the nitrile functionality took place, which in the presence of a suitable (chiral) diamine, ring-closed to give the stable cyclic aminal **61** in a stereoselective fashion.

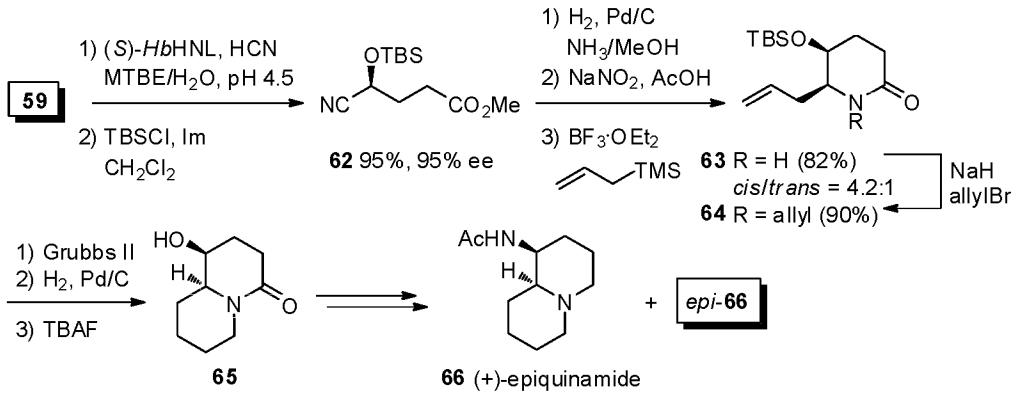
Scheme 1.12 *Asymmetric synthesis of 5-hydroxypiperidone-derived N,N-acetals.*



A few years later, the same group reported the chemoenzymatic synthesis of the natural product (+)-epiquinamide **(66)** and elucidated its absolute stereochemistry.[19] Key steps in this sequence involved chemoenzymatic enantioselective cyanohydrin formation starting from succinic semialdehyde **59** using (*S*)-selective HNL from *Hevea brasiliensis* (*Hb*HNL)

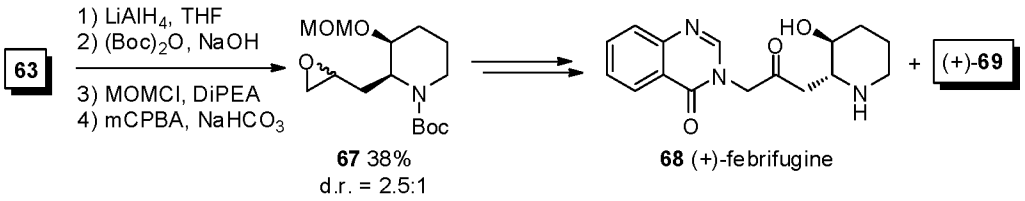
delivering the (*S*)-cyanohydrin in excellent yield and enantiopurity (Scheme 1.13). Reductive amination followed by diazotation of the key *N,N*-acetal and subsequent transformation of the resulting *N*-acyliminium ion precursor delivered **63** in 82% overall yield (4.2:1 *cis*:*trans*). After some standard conversions, intermediate **65** containing the core skeleton, was converted into (+)-epiquinamide (**66**) and its epimer *epi*-**66**.

Scheme 1.13 *Chemoenzymatic synthesis of (+)-epiquinamide (66) and epi-66.*



In a recent publication, the authors used similar methodology as a starting point for the synthesis of (+)-febrifugine (**68**) and (+)-isofebrifugine (**69**) (Scheme 1.14).[20]

Scheme 1.14 *Chemoenzymatic total synthesis of (+)-febrifugine (68) and (+)-isofebrifugine (69).*



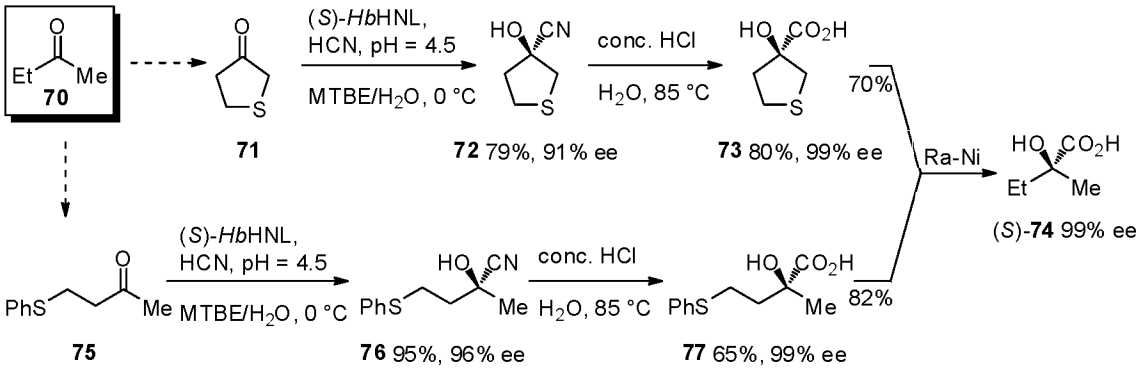
1.2.2 Hydrolysis of the nitrile group

1.2.2.1 Synthesis of α-hydroxy acids

Enantiopure α-hydroxycarboxylic acids are versatile building blocks in organic synthesis.[2a,c,21] As part of the research on asymmetric HNL-catalyzed cyanide addition to saturated heterocyclic ketones, the Griengl group investigated the chemoenzymatic synthesis of (*S*)-2-hydroxy-2-methylbutyric acid (**74**), an important intermediate in the synthesis of a

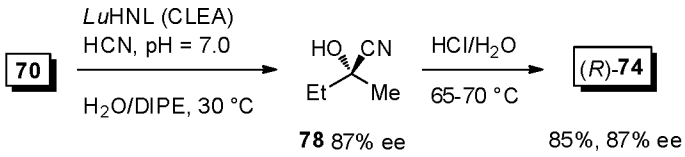
COX inhibitor (Scheme 1.15).[22] Preliminary investigations into the biocatalytic cyanide addition on 2-butanone (**70**) by employing (*S*)-selective *Hb*HNL provided the corresponding cyanohydrin in only low enantiomeric excess as a result of the low enantiopreference between the ethyl and methyl group in the active site of the enzyme. Therefore, by using 3-tetrahydrothiophen-3-one (**71**) and 4-phenylthiobutan-2-one (**75**) as masked equivalents for 2-butanone (**70**) in the cyanohydrin synthesis, both substituents flanking the carbonyl group were sufficiently distinguished providing the cyanohydrins **72** and **76** in high enantiopurity. Next, both cyanohydrins were hydrolyzed in good yield using concentrated hydrochloric acid affording the hydroxy acids **73** and **77** as single enantiomeric products after recrystallization. Desulfurization with Raney nickel transformed the thiols into the desired (*S*)-2-hydroxy-2-methylbutyric acid ((*S*)-**74**).

Scheme 1.15 *HNL-catalyzed chemoenzymatic synthesis of (S)-2-hydroxy-2-methylbutyric acid (74).*



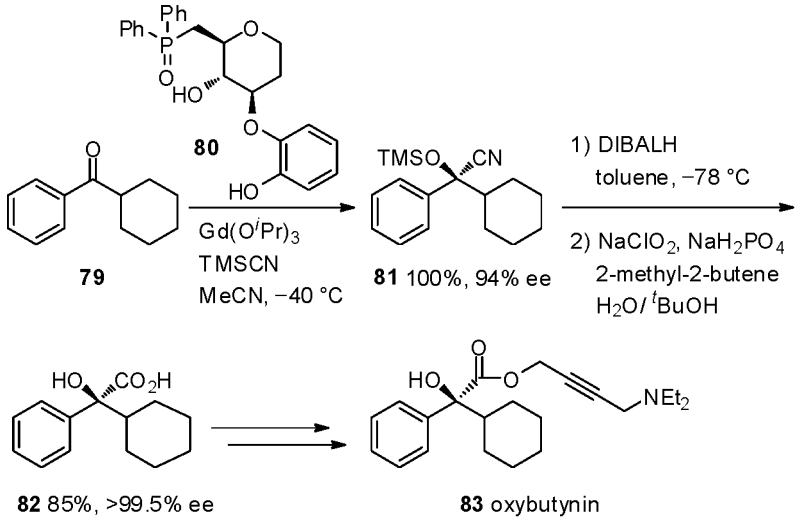
Sheldon *et al.* developed a straightforward enzymatic hydrocyanation process based on immobilized HNL (*Lu*HNL CLEA).[23] (*R*)-2-Butanone-derived cyanohydrin **78** was synthesized on a preparative scale upon catalysis by *Lu*HNL with 87% ee (Scheme 1.16). The crude cyanohydrin **78** was readily obtained by simple filtration of the catalyst and evaporation of the volatiles. Acidic hydrolysis afforded (*R*)-2-hydroxy-2-methylbutyric acid ((*R*)-**74**) in 85% yield and 87% ee.

Scheme 1.16 *LuHNL-CLEA based synthesis of (R)-2-hydroxy-2-methylbutyric acid.*



A practical procedure for the synthesis of an important intermediate of the muscarinic receptor antagonist (*S*)-oxybutynin (**83**) and analogues thereof was reported by Shibasaki and co-workers (Scheme 1.17).[24] The key step in this sequence concerned a catalytic asymmetric cyanosilylation of commercially available cyclohexyl phenyl ketone (**79**). The reaction was performed at 100 g scale and proceeded in quantitative yield and high selectivity (94% ee) under the influence of an *in situ* generated gadolinium catalyst. Next, a two-step reduction–oxidation approach was used to arrive at the carboxylic acid **82**. In this case, other more general methods, such as acidic hydrolysis or alcoholysis and basic conditions proved to be unsuccessful. Finally, recrystallization gave an enantiomerically pure precursor for the oxybutynin (**83**) synthesis.

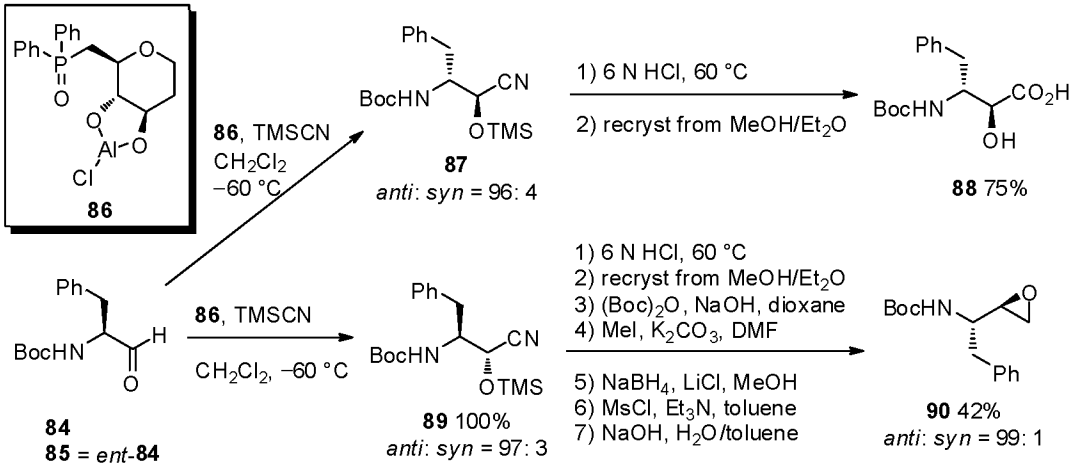
Scheme 1.17 *Enantioselective synthesis of oxybutynin (83).*



Pseudopeptides containing 3-amino-2-hydroxycarboxylic acids or 3-amino-2-hydroxy-amines are essential components in many pharmaceutically active compounds. The Shibasaki-group also reported the synthesis of some important chiral building blocks of a HIV protease

inhibitor and a β_3–adrenergic receptor agonist *via* stereoselective organocatalyzed cyanosilylation (Scheme 1.18).[25] By using a catalytic system based on Lewis acid–Lewis base bifunctional catalysts **86**, they successfully succeeded in diastereoselective cyanosilylation in high yield and stereoselectivity.

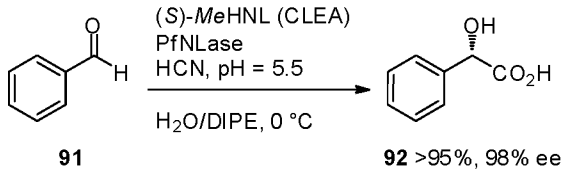
Scheme 1.18 *Stereoselective cyanosilylation using a bifunctional catalyst.*



Most methods for the preparation of α-hydroxy acids rely on chemical hydrolysis of the nitrile functionality. Chemical hydrolysis of nitriles is well established, but requires relatively harsh conditions necessitating the protection of sensitive functional groups. A more elegant approach is to enantioselectively prepare the cyanohydrins under hydroxynitrile lyase-mediated conditions and subsequently convert them with the help of non-selective nitrilases into the corresponding carboxylic acids.

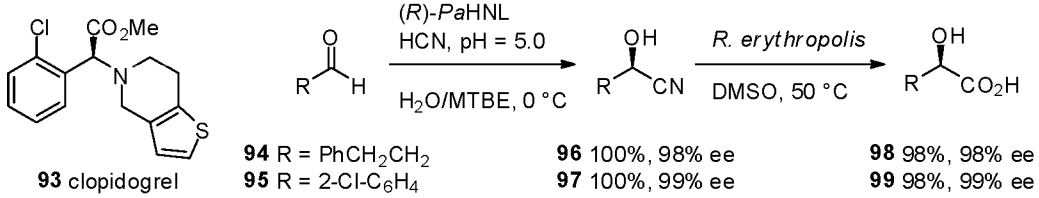
The latter approach has been used in the group of Sheldon,[26] by combining an immobilized (*S*)-selective oxynitrilase from *Manihot esculenta* and a non-selective nitrilase from *Pseudomonas fluorescens* EBC 191 in a one-pot enzymatic cascade (Scheme 1.19). The final carboxylic acid (*S*)-**92** was obtained in high yield and excellent enantiopurity.

Scheme 1.19 *Enzymatic cascade reaction for the synthesis of (S)-mandelic acid.*



Two important pharmaceutical intermediates, (*R*)-2-chloromandelic acid (**99**), the chiral intermediate of the anti-thrombotic agent clopidogrel (**93**), and (*R*)-2-hydroxy-4-phenylbutyric acid (**98**), the key building block for the synthesis of several ACE-inhibitors, were efficiently prepared on gram scale in two steps using a biocatalytic approach (Scheme 1.20).[27] Employing enantiopure cyanohydrins **96** and **97**, which were readily prepared using hydroxynitrile lyases and a highly active nitrile hydratase/amidase enzyme system present in *Rhodococcus erythropolis*, the desired hydroxy acids **98** and **99** were obtained in high optical purity (ee >98%) and isolated yield (98%).

Scheme 1.20 *Biocatalytic synthesis of enantiopure α-hydroxy acids.*

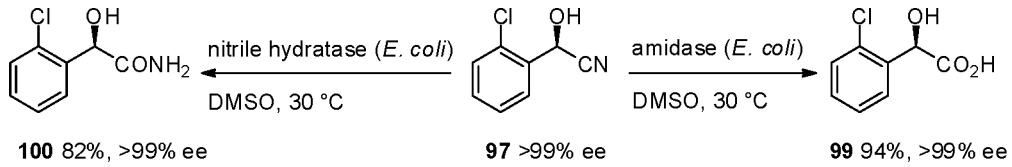


At the same time Sheldon *et al.* developed a similar industrially viable synthesis of (*R*)-2-chloromandelic acid (**99**) providing the cyanohydrin **97** in a high yield of 98% and satisfactory ee of 90%.[28] Subsequent chemical nitrile hydrolysis in refluxing concentrated HCl followed by recrystallization furnished the target molecule **99** in an excellent ee of 99%.

1.2.2.2 Synthesis of α-hydroxy amides

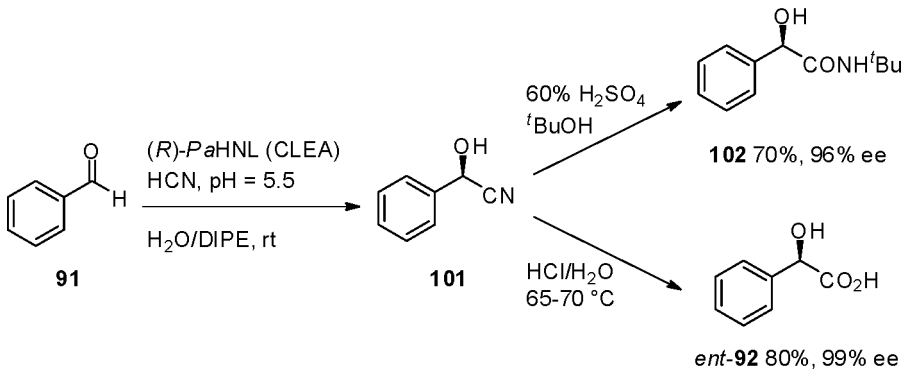
Soon after, the Griengl group developed an enzymatic hydrolysis process for cyanohydrins by using the same recombinant nitrile hydratase and amidase from *Rhodococcus erythropolis*, but now cloned and expressed in *E. coli*.[29] By separation of the nitrile hydratase and amidase they succeeded in using the single recombinant enzymes for successful synthesis of both the corresponding α-hydroxy acid **99** and amide **100** with retention of optical purity (Scheme 1.21).

Scheme 1.21 *Enzymatic hydrolysis using recombinant enzymes.*



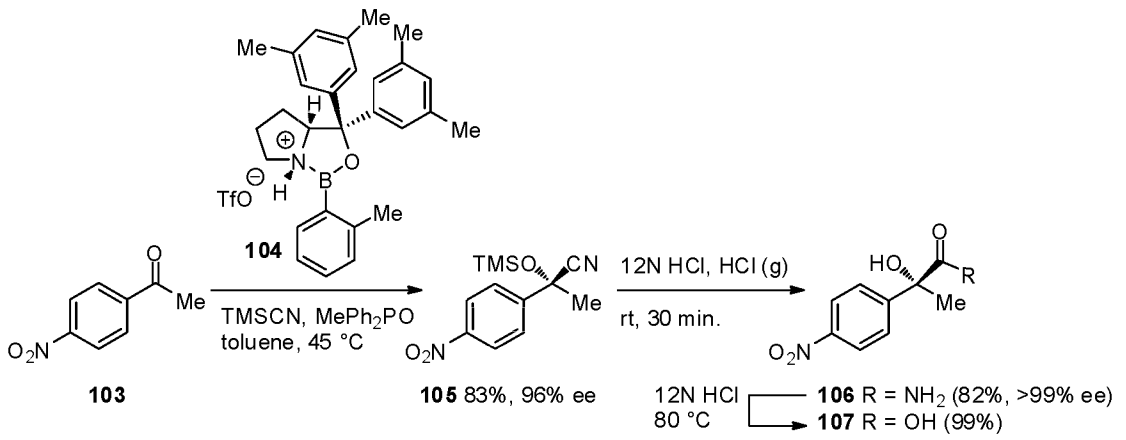
Starting from benzaldehyde **91**, the Sheldon group also developed a cost-efficient process using immobilized *Pa*HNL for enantioselective cyanohydrin formation delivering the crude mandelonitrile **101** which was further derivatized in a second step without intermediate purification (Scheme 1.22).[30]

Scheme 1.22 *PaHNL-CLEA based hydrocyanation and derivatization.*



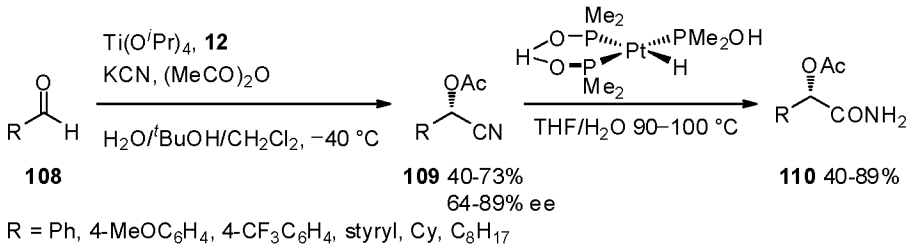
In 2005, Corey *et al.* showed a highly efficient asymmetric cyanosilylation of different functionalized methyl ketones **103** using a catalytic amount of the chiral oxazaborolidinium salt **104** (Scheme 1.23).[31] This route gives fast access to the synthesis of many interesting chiral building blocks such as the atrolactic acids **107** by hydrolysis of the nitrile functionality.

Scheme 1.23 *Synthesis of (R)-4-nitroatrolactic acid (**107**).*



Application of chiral salen complex **12** in combination with $Ti(O^iPr)_4$ was described by North *et al.*[32] They used a two-step catalytic approach for the asymmetric synthesis of the α-acetoxy amides **110** (Scheme 1.24). Treatment of both aliphatic and aromatic aldehydes with chiral titanium salen complexes catalyst systems delivered the corresponding cyanohydrins **109** in moderate to good yield and ee. Consecutive hydrolysis with the shown palladium(II) complex under neutral conditions led to smooth conversion into the α-acetoxy amides **110** without any loss of optical purity.

Scheme 1.24 *Synthesis of α-hydroxy amides.*

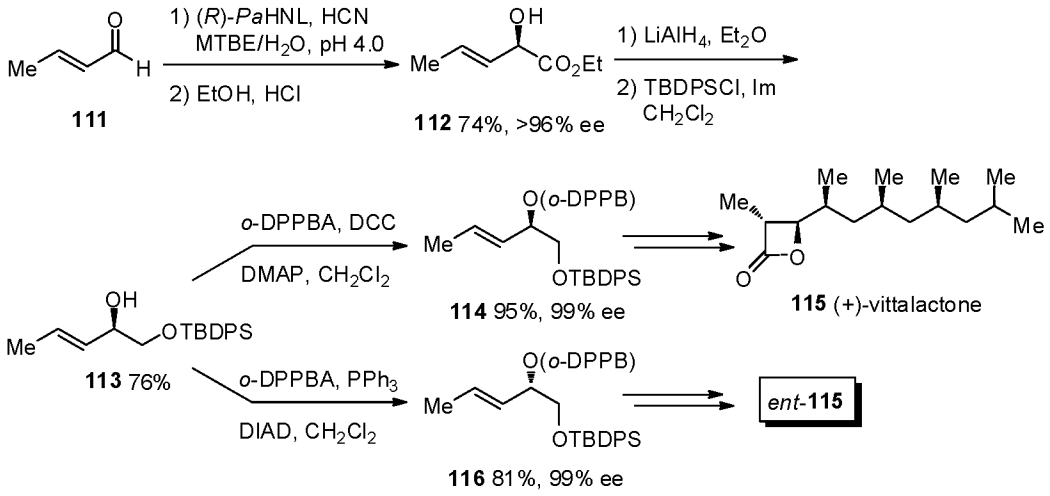


1.2.2.3 Synthesis of α-hydroxy esters

In the search for a environmentally benign plant defense strategies to protect cucurbits from the striped cucumber beetle *Acalymma vittatum*, researchers developed a chemoenzymatic approach for the synthesis of the natural product (+)-vittalactone (**115**) and its enantiomer *ent*-**115**.[33] The enantioselective (*R*)-*Pa*HNL catalyzed chemoenzymatic cyanohydrin formation on crotonaldehyde (**111**) was a key reaction step in the synthesis and delivered the corresponding

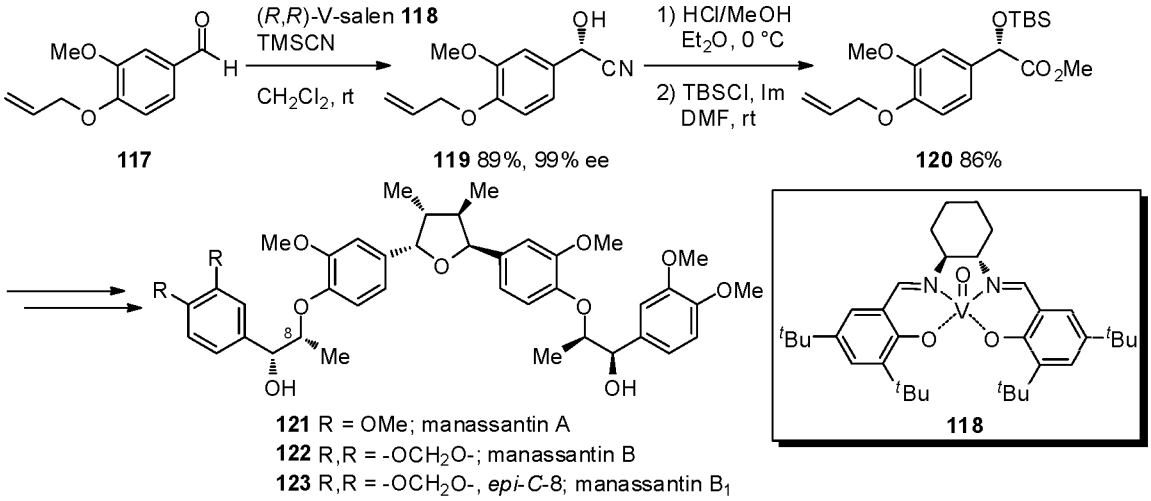
cyanohydrin **112** in high enantiomeric purity of >96% (Scheme 1.25).[34] Subjection of the crude cyanohydrin to a Pinner reaction followed by reduction of the ester moiety, furnished upon protection, silyl ether **113** in good yield and with retention of the optical purity. Applying the standard Steglich esterification protocol with *o*-diphenylphosphanylbenzoic acid (*o*-DPPBA) provided the corresponding ester in quantitative yield and with improved ee after crystallization. For obtaining the (*S*)-enantiomer **116** the authors chose to subject silyl ether **113** to Mitsunobu conditions thereby using *o*-DPPBA itself as the nucleophile. Crystallization afforded **116** as a single enantiomer and served as an intermediate in the total synthesis of *ent*-**115**.

Scheme 1.25 *Chemoenzymatic synthesis of (+)-vittalactone (**115**) and ent-**115**.*



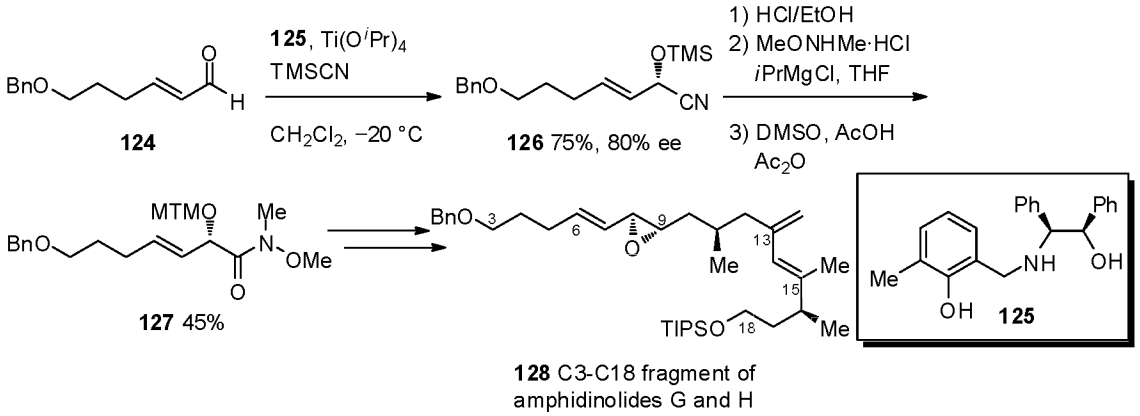
The group of Hanessian developed a stereoselective total synthesis of natural products manassantins A, B, and B_1 (**121**–**123**), and saucerneol starting from the enantiopure cyanohydrin **119** (Scheme 1.26).[35] A vanadium-catalyzed asymmetric hydrocyanation with salen-complex **118** developed by Belokon *et al.*[36] delivered cyanohydrin **119** in 89% yield and 90% ee, which upon recrystallization was improved to 99%. Methanolysis of the nitrile under acidic conditions and subsequent esterification furnished methyl ester **120** as precursor for the total synthesis of the manassantin natural products.

Scheme 1.26 *Catalytic asymmetric total synthesis of manassantins.*



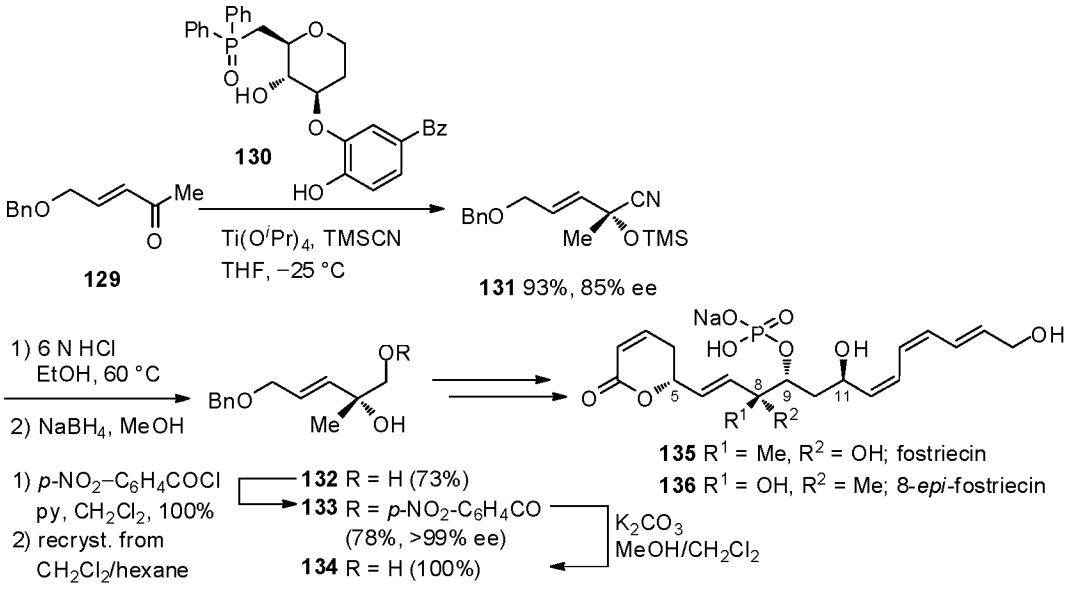
The group of Crews *et al.* developed a stereoselective synthesis of the C3-18 fragment of amphidinolides G and H (**128**), which were isolated from the symbiotic marine dinoflagellate *Amphidinium* sp., and exhibited extremely potent cytotoxic activity against several types of cancer cells.[37] Starting from the benzyl-protected aldehyde **124**, an asymmetric cyanosilylation method developed by Feng and co-workers[38] was used to access the TMS-protected cyanohydrin **126** (Scheme 1.27). Exposure to acidic ethanolysis, followed by amidation of the corresponding ester to generate the Weinreb amide and protection of the hydroxyl group as the methylthio methyl ether completed the synthesis of building block **127** in 45% yield over three steps.

Scheme 1.27 *Synthesis of the C3-18 fragment of amphidinolides G and H.*



An efficient strategy for the synthesis of the natural antibiotic fostriecin (**135**) and its analogue 8-*epi*-fostriecin (**136**) was designed by Shibasaki *et al.*[39] As starting material was chosen for benzyl-protected ketone **129** which was subjected to a catalytic asymmetric cyanosilylation using a chiral titanium complex derived from ligand **130** and $Ti(O^iPr)_4$ affording the (*R*)-cyanohydrin **131** in excellent yield and high enantioselectivity (Scheme 1.28). Transformation of **131** into primary alcohol **134** *via* ethanolysis and $NaBH_4$ reduction followed by recrystallyzation, and subsequent hydrolysis of the *p*-nitrobenzoyl ester furnished enantiopure pure **134** (>99% ee). This key intermediate **134** was then converted into the natural product fostriecin (**135**). The synthesis of its analogue 8-*epi*-fostriecin (**136**), following a similar procedure as for the fostriecin (**135**) synthesis, commenced with the (*S*)-selective cyanosilylation of **129** using ligand **80** in combination with gadolinium triisopropoxide.

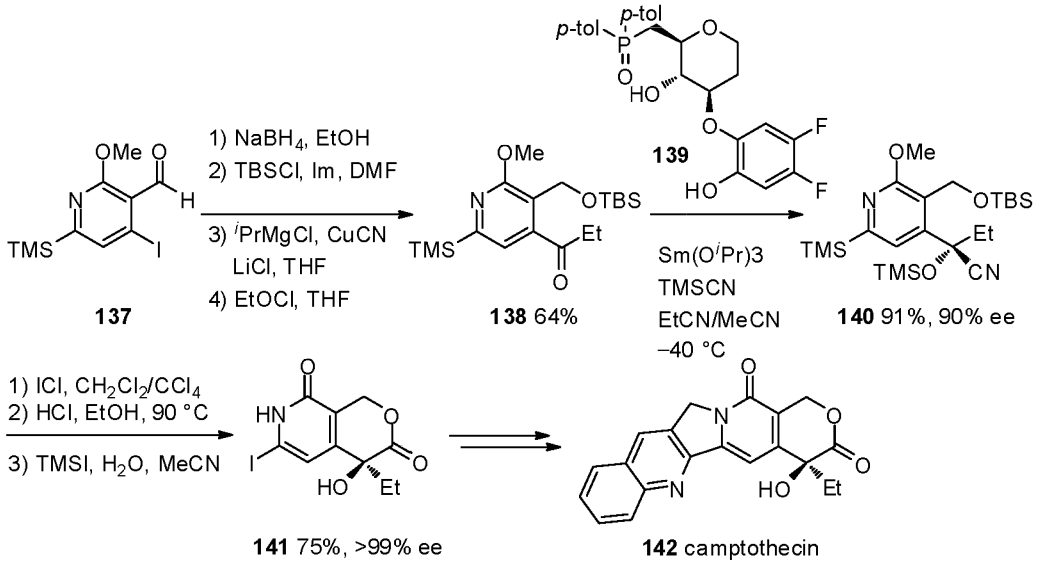
Scheme 1.28 *Enantioselective catalytic total synthesis of fostriecin (135) and 8-epi-fostriecin (136).*



Shibasaki and co-workers showed the application of ligand **139** in combination with samarium triisopropoxide in an efficient enantioselective route of camptothecin (**142**), a structurally related analogue of the approved anti-cancer agents topotecan and irinotecan.[40] After extensive investigation, it was found that the D-glucose-based ligand **139** in the presence of samarium triisopropoxide was most suitable for obtaining intermediate **140** in a high yield of 91% and a fairly good ee of 90% (Scheme 1.29). After ICl-induced

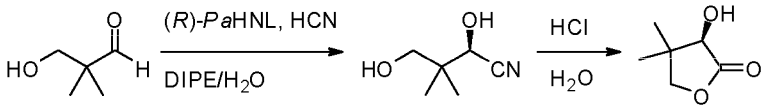
iododesilylation, direct lactonization was performed under acidic conditions, followed by demethylation to give α-hydroxyl lactone **141**, which at this stage could be obtained in fully enantiopure form after recrystallization. Similar approach to access the target camptothecin (**142**) was also described by Kanazawa and co-workers.[41]

Scheme 1.29 *Asymmetric camptothecin key intermediate synthesis.*



The application of (*R*)-hydroxnitrile lyases also enabled a simple chemoenzymatic approach to (*R*)-pantolactone **145**, which is an important precursor for the synthesis of (*R*)-pantothenic acid (vitamine B_5) and its provitamin (*R*)-panthenol. In recent years, several efforts have been made to optimize the enantioselective enzymatic addition of HCN to hydroxypivaldehyde (**143**). However, so far this process was accompanied by using large amounts of highly purified enzyme and thus making application on industrial scale rather unattractive.[42] For this reason, Wlostowski *et al.* set up an experimental design to find the optimal conditions and carried out an asymmetric hydrocyanation of hydroxypivaldehyde (**143**) catalyzed by an (*R*)-selective HNL from defatted kernel meal from almonds, apples, and plums without isolating it from the original material.[43] The resulting cyanohydrin **144** was *in situ* hydrolyzed affording (*R*)-pantolactone **145** in 74% yield over three steps but in a low ee of 30% (Scheme 1.30). A few years later, a similar strategy was applied by Glieder *et al.*,[44] who made use of site-saturation mutagenesis (SSM) of *Pa*HNL5 resulting in a powerful catalyst for highly enantioselective conversion (>97% ee) of **144** in quantitative yield.

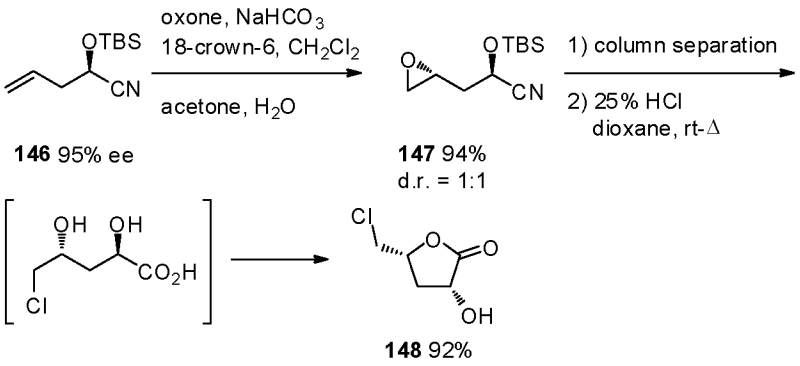
Scheme 1.30 *Chemoenzymatic synthesis of (R)-pantolactone **145**.*



143 **144** **145** 74%, 30% ee

Orru *et al.* reported the use of γ,δ-unsaturated TBS-protected cyanohydrins **146** in a one-pot four-reaction hydrolysis-induced lactonization cascade (Scheme 1.31).[45] In this method, cyanohydrin **146** was obtained by employing either (*R*)- or (*S*)-selective HNL-catalyzed hydrocyanation on the corresponding β,γ-unsaturated aldehydes, directly followed by protection. Cyanohydrin **146** subsequently underwent epoxidation with Oxone® resulting in a 1:1 ratio of diastereoisomers **147**, which were separated by column chromatography. Surprisingly, the hydrolysis-induced lactonization did not afford the anticipated 5'-OH-substituted lactones. Instead, the corresponding 5'-chloro-substituted lactone **148** was formed as a result of attack of the chloride ion onto the primary carbon atom of epoxide **147**. In this way, enantiopure 5'-chloro-3'-deoxyribolactones **148** were accessed *via* a short and efficient synthesis.

Scheme 1.31 *Asymmetric synthesis of chloromethyllactones.*



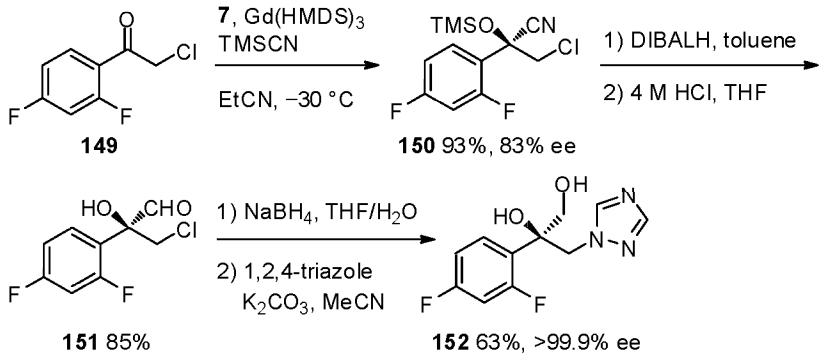
146 95% ee **147** 94% d.r. = 1:1 **148** 92%

1.2.2.4 Synthesis of α-hydroxy aldehydes

Because of their broad antifungal activity and low toxicity profile, triazole-containing antifungal agents are important in the treatment of infectious diseases. For this reason Shibasaki *et al.* developed a short and efficient synthetic pathway for antifungal drug intermediates making use of an enantioselective cyanosilylation of ketone **149** catalyzed by a

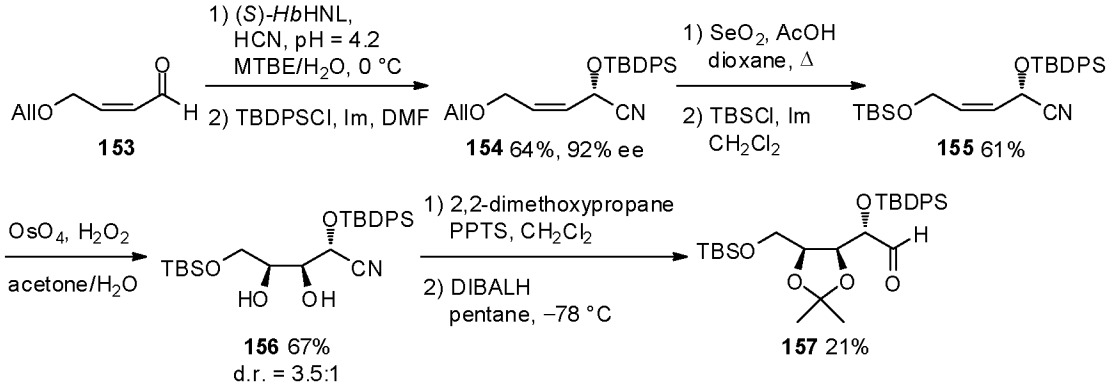
gadolinium-ligand system as the key reaction (Scheme 1.32).[46] Reduction of the nitrile functionality and acidic work-up, followed by a second reduction of the formed aldehyde **151** and substitution of the chloride with triazole anion, delivered the triazole antifungal agent **152**.

Scheme 1.32 *Catalytic asymmetric synthesis of triazole based antifungal agents.*



Owing to the general pharmaceutical importance of L-sugars, Griengl *et al.* published a novel approach toward pentoses (Scheme 1.33).[47] The key steps in this route involved enzyme-catalyzed asymmetric HCN addition followed by asymmetric dihydroxylation. The starting α,β-unsaturated aldehyde **153** was readily prepared from (*Z*)-2-buten-1,4-diol. The best results in the (*S*)-*Hb*HNL-catalyzed reaction were obtained when an allyl-protecting group was used. To prevent chemoselectivity problems in the dihydroxylation step, the allyl protecting group was replaced by a TBS group. Additionally, the bulky TBDPS group was introduced to maximize the stereodirecting effect of the substituents at the chiral center in the dihydroxylation reaction. A catalytic amount of OsO_4 in combination with hydrogen peroxide as the stoichiometric oxidant gave the most satisfactory results and delivered diol **156** in 67% yield as a 3.5:1 mixture of diastereoisomers. Finally, diol protection and nitrile reduction gave the pentose precursor **157**.

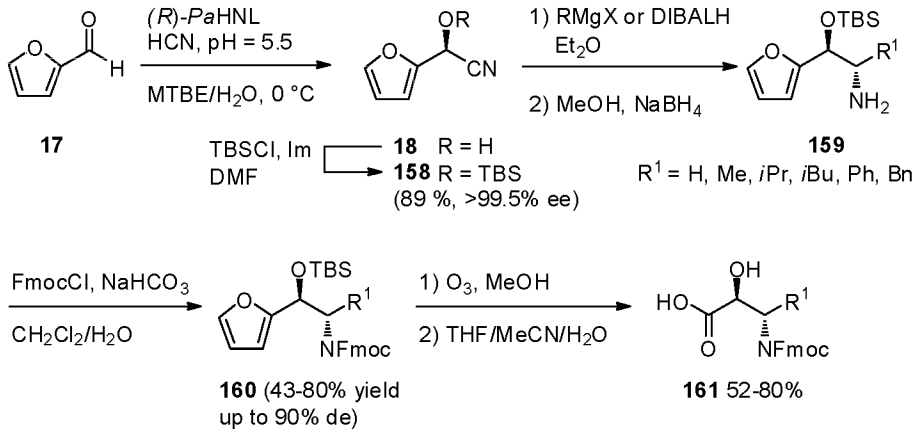
Scheme 1.33 *Asymmetric synthesis of pentoses.*



1.2.3 Grignard addition

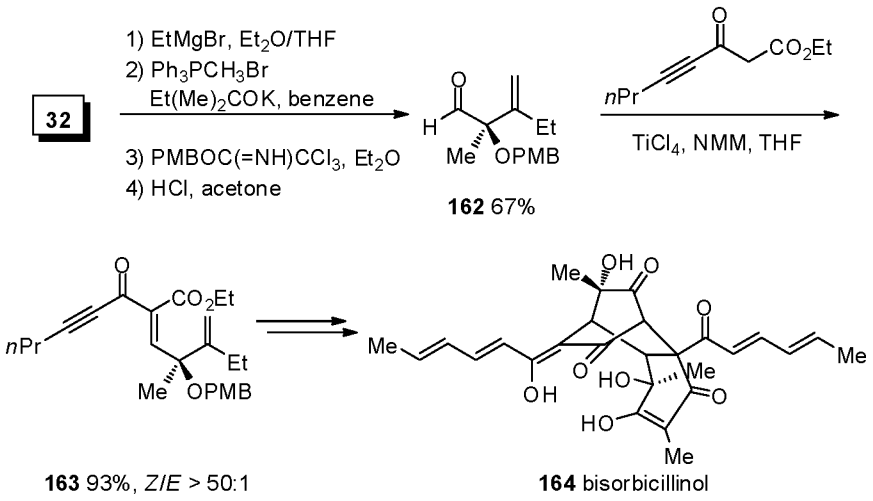
The van der Gen group developed a convenient general route for a fully stereoselective chemoenzymatic synthesis of α-hydroxy-β-amino acid derivatives starting from furfural (**17**) (Scheme 1.34).[48] Thus, **17** was readily converted into the corresponding (*S*)-cyanohydrin in excellent enantioselectivity in the presence of the (*R*)-selective *Pa*HNL.[49] TBS protection of the hydroxyl group proceeded in high yield, followed by introduction of the amino acid side chain *via* a one-pot two-step process involving a Grignard addition–reduction sequence. In case of α-hydroxy-β-glycine (R^1 = H), a double reduction process was carried out. Subsequent Fmoc-protection of the crude ethanolamines delivered the products **160** in good yield and high diastereoselectivity. Finally, oxidation of the furan-ring under ozonolysis conditions with concomitant TBS-removal furnished the corresponding carboxylic acids **161** in one step.

Scheme 1.34 *Chemoenzymatic asymmetric synthesis of α-hydroxy-β-amino acids.*



Deng *et al.* developed the first enantioselective total synthesis of bisorbicillinol (**164**), and its structural analogues bisorbicillinolide and bisorbibutenolide.[50] Starting from (*R*)-cyanohydrin **32** which on multigram scale in quantitative yield and 92% ee (Scheme 1.35). Grignard addition, Wittig olefination, followed by protection of the hydroxyl functionality and acidic hydrolysis of the acetal smoothly provided the precursor **162** in 67% yield. Knoevenagel condensation of **162** with an acetylene-containing β-keto ester in the presence of NMM gave **163** and proceeded with excellent yield and *Z*-selectivity (*Z*/*E* ratio > 50:1). After several transformations, final [4+2] dimerization completed the synthesis of bisorbicillinol (**164**).

Scheme 1.35 *Asymmetric synthesis of bisorbicillinol (**164**).*



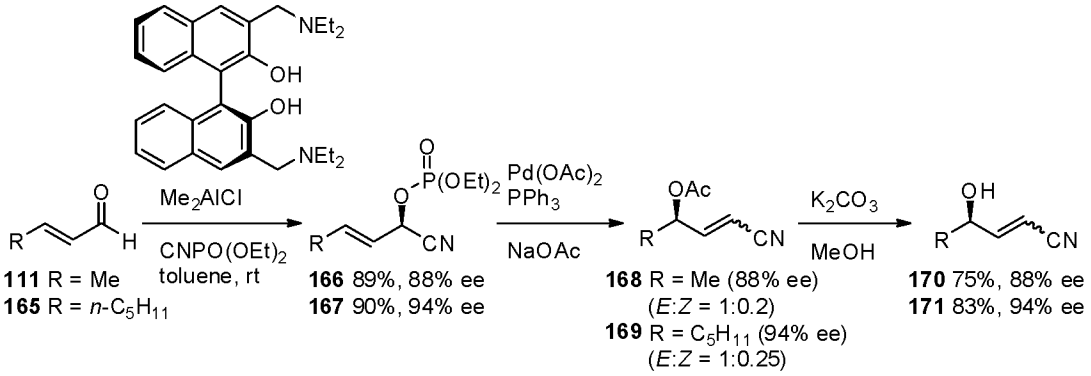
1.3 Modification of the alcohol group

1.3.1 Allylic substitution

Saá *et al.* were the first to report an enantioselective cyanophosphorylation of aldehydes catalyzed by a bifunctional catalyst system.[51] To demonstrate the application of the resulting building blocks, the cyanohydrin *O*-phosphates **166** and **167** were converted into the corresponding *O*-phosphorylated hydroxy esters, β-amino alcohols or into γ-cyanoallylic alcohols **168** and **169** by subjection to a palladium(0)-catalyzed stereospecific [3,3] sigmatropic rearrangement, followed by basic hydrolysis of the acetates (Scheme 1.36). The corresponding γ-cyanoallylic alcohols **168** and **169** were obtained as separable *E*/*Z*-mixtures in a ratio of 1:0.2 and 1:0.25, depending on the nature of the phosphine. The *E*-selectivity was

a result of the double inversion (net retention) caused by the favored affinity of palladium for the nitrile group, while the *Z*-products were formed *via* inversion of configuration. In all cases no loss of enantiopurity was observed.

Scheme 1.36 *Palladium-catalyzed allylic substitution of cyanohydrin O-phosphates.*

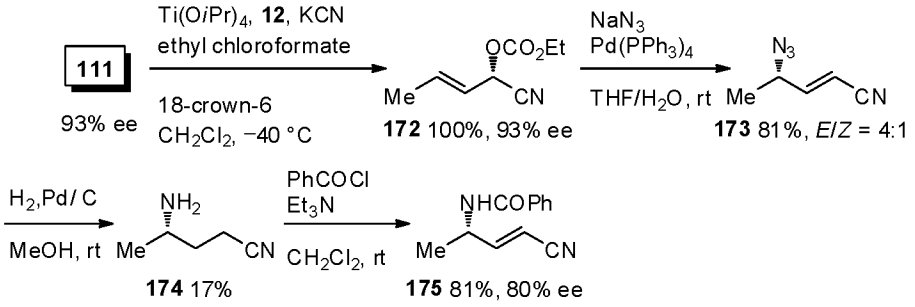


Cyanophosphates proved also viable building blocks in other applications as was shown by the synthesis of the two structurally related natural products (–)-aegeline and (–)-tembamide, both showing high hypoglycaemic activity.[52] Moreover, the use of the same catalytic system appeared also an effective catalyst in promoting a one-pot synthesis of enantioselective *O*-methoxycarbonyl cyanohydrins.[53] In the latter approach, the same group performed comprehensive studies on palladium- and iridium-catalyzed allylic substitution reactions of β,γ-unsaturated cyanohydrin *O*-phosphates and their *O*-carbamate equivalents,[54] and investigated copper-mediated allylic substitution reactions.[55] In contrast to the palladium-catalyzed sequence which only allows for soft nucleophiles, the latter approach has the advantage of being compatible with hard nucleophiles such as Grignard reagents.

North *et al.* developed an enantio- and diastereoselective approach for the synthesis of cyanohydrin carbonates in the presence of chiral titanium(salen) complex and potassium cyanide as co-catalyst.[56] After application of optimal conditions on α,β-unsaturated aldehyde **111** to obtain the corresponding β,γ-unsaturated cyanohydrin **172**, they demonstrated the utility of the latter adduct by reacting **172** with sodium azide and a palladium catalyst (Scheme 1.37). Compound **173** was formed as a mixture of isomers in a ratio of 4:1 in favor of the *E*-olefin. Hydrogenation of the double bond followed by benzoylation to verify the enantiomeric excess provided the nitrile derivative **175** in an optical purity of 80%. This

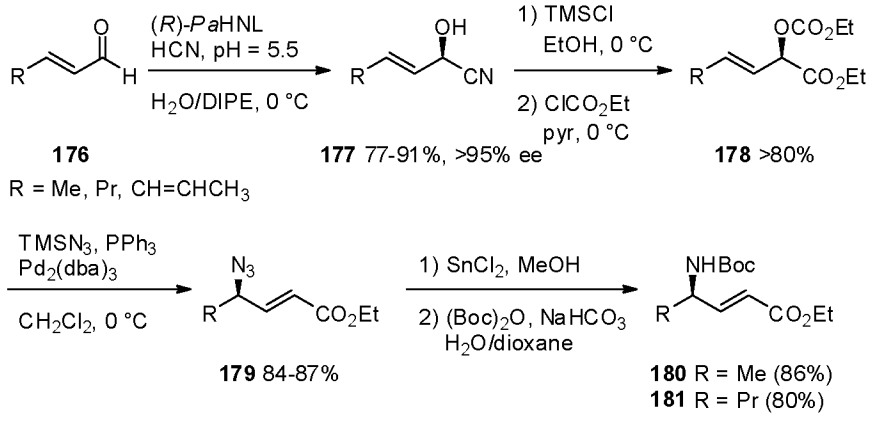
observation was in agreement with the findings on partial racemization of substrates during palladium-catalyzed allylic substitution, as previously reported by Deardorff.[57]

Scheme 1.37 *Derivatization of β,γ-unsaturated cyanohydrins.*



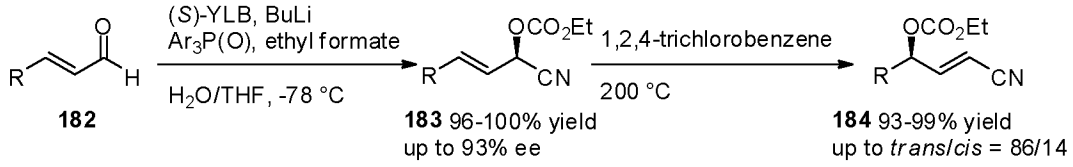
In early investigations, the group of Chen demonstrated that racemic unsaturated carbonates are excellent synthons which can undergo palladium(0)-catalyzed allylic substitutions in a completely regiospecific manner affording the resulting γ-azido-α,β-unsaturated nitriles as *cis/trans* mixtures. Based on these findings, in a more recent study, they showed that enantiopure variants of these substrates could lead to (*E*)-vinologous (*R*)-amino esters (Scheme 1.38).[58] *Via* a *Pa*HNL-catalyzed asymmetric hydrocyanation with HCN in a biphasic mixture of buffer at pH 5.5 and diisopropyl ether the chirality was installed at the aldehyde carbon atom in good yield and >95% ee. After successful transformation of **177** into the corresponding ester carbonates **178**, they were able to synthesize the desired products **179** with retention of configuration and exclusive *E*-double bond geometry.

Scheme 1.38 *Enantioselective synthesis of E-vinylogous (R)-amino esters.*



In 2002, the group of Shibasaki reported a novel catalytic asymmetric cyanation–ethoxycarbonylation reaction of aldehydes with ethyl formate in the presence of a YLi_3-tris(binaphthoxide) complex (YLB).[59] This elegantly provided direct access to optically active cyanohydrin carbonates **183** in excellent yield and high ee (Scheme 1.39). In order to demonstrate their potential as unique chiral building blocks, the allylic cyanohydrins **183** were converted into the chiral γ-oxy-α,β-unsaturated nitriles **184** with retention of configuration *via* a [3,3]-sigmatropic rearrangement under thermal conditions. When Lewis acids were used to promote the rearrangement reaction, higher *trans*/*cis* ratio's of up to >98:2 were obtained, however, partial racemization was also observed.

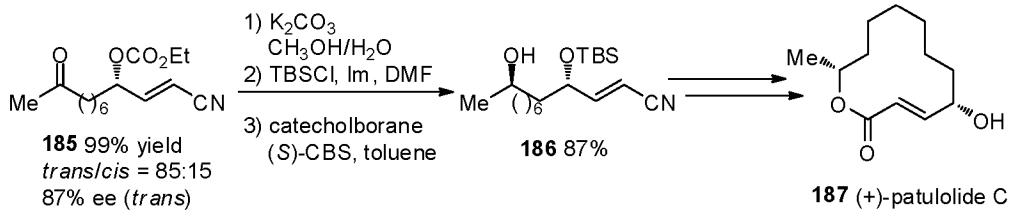
Scheme 1.39 *Synthesis of chiral γ-oxy-α,β-unsaturated nitriles.*



R = $CH_3(CH_2)_2$, $Ph(CH_2)_2$, Ph, *c*-C_6H_{11}

To further elaborate the scope of this two-step conversion, a concise catalytic enantioselective total synthesis of the natural product (+)-patulolide C (**187**) was developed.

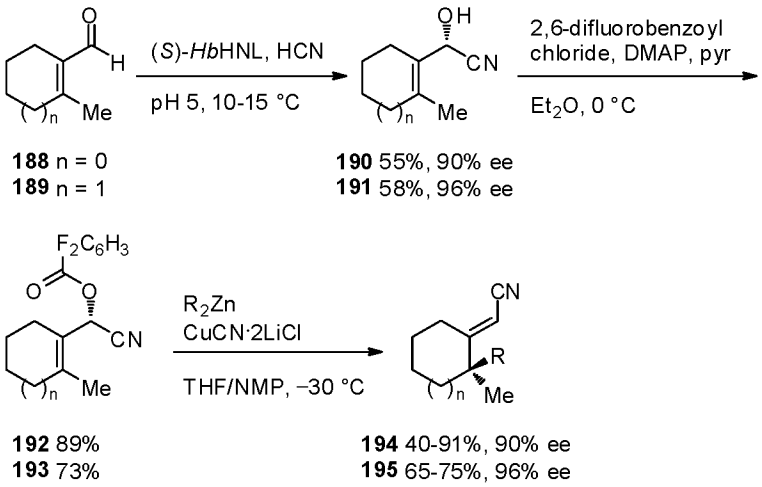
Scheme 1.40 *Catalytic asymmetric total synthesis of (+)-patulolide C (187).*



Knochel *et al.* investigated a highly stereo- and regioselective Cu(I)-mediated S_N2' allylic substitution reaction of enantiopure difluorobenzoylated allylic cyanohydrins with diorganozinc reagents (Scheme 1.41).[60] The enantioselective (*S*)-*Hb*HNL-catalyzed HCN addition on aldehydes **188** and **189** in a monophasic citrate buffer system provided the corresponding cyanohydrins **190** and **191** in acceptable yield and ee's of 90 and 96% for n = 0 and n = 1, respectively. Subsequent esterification with 2,6-difluorobenzoyl chloride afforded

both esters **192** and **193** without racemization. Allylic substitution on ester **193** occurred in excellent diastereoselectivity, for primary alkyl substituents, while more sterically hindered nucleophiles such as *i*-Pr_2Zn or *c*-Hex_2Zn were not selective. On the contrary, reaction of cyclopentyl cyanobenzoate **192** did not suffer from these limitations and reacted smoothly with various diorganozinc reagents providing the α,β-unsaturated nitriles **194** in excellent diastereoselectivity.

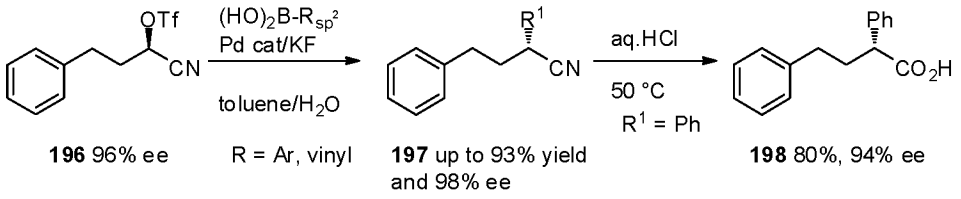
Scheme 1.41 *Cu(I)-mediated allylic substitution on difluorobenzoylated cyanohydrins.*



1.3.2 Stereospecific Suzuki cross-coupling reactions

Inspired by the fact that suitably functionalized α-cyanohydrins are known to undergo displacement by a variety of nucleophiles, Falck *et al.* exploited the traditional Suzuki cross-coupling reaction on cyanohydrin triflates **196** (Scheme 1.42).[61] After extensive optimization of the reaction parameters, they were eventually able to couple a functionalized sp^3-hybridized stereogenic carbon to aryl, heteroaryl, and vinyl boronic acids in a stereospecific manner. The coupling proceeded with complete inversion of configuration. Further manipulation, *e.g.* hydrolysis of the resulting nitrile was performed to provide facile and fast access to various interesting organic building blocks (*e.g.* **198**).

Scheme 1.42 *Stereospecific Suzuki cross-coupling of cyanohydrin triflates.*

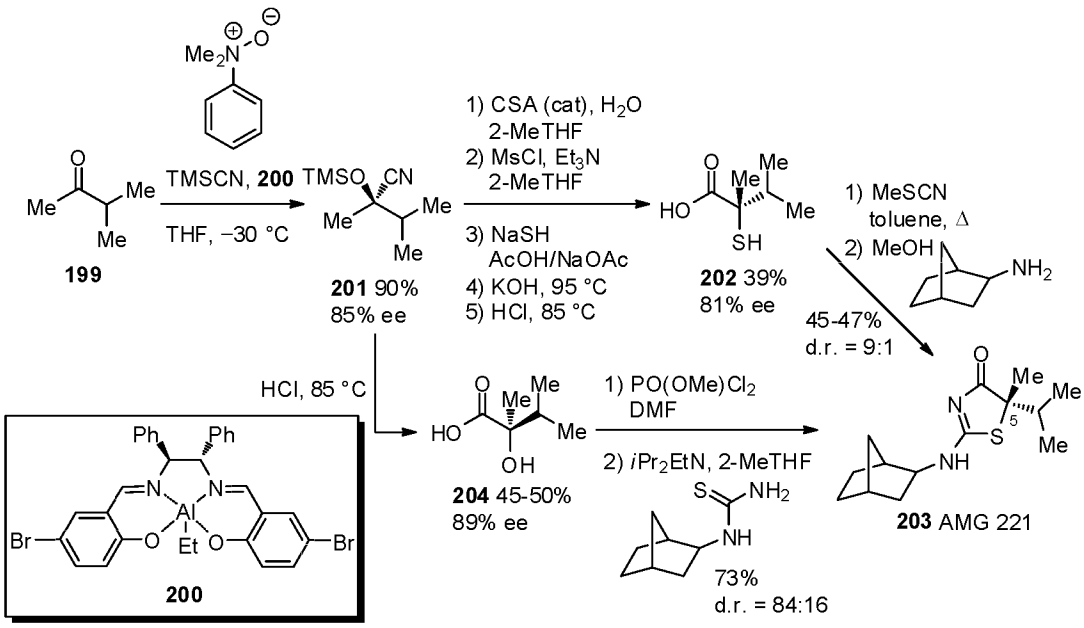


196 96% ee R = Ar, vinyl **197** up to 93% yield and 98% ee **198** 80%, 94% ee

1.3.3 Substitution by Mitsunobu reaction

The group of Faul *et al.* developed two asymmetric syntheses of 2-aminothiazolone AMG 221 (**203**), a potential therapeutic agent for the treatment of type 2 diabetes.[62] The enantioselective preparation of TMS-protected cyanohydrins **201** was accomplished using the chiral aluminum salen complex **200** and *N*,*N*-dimethylaniline *N*-oxide (Scheme 1.43). From there, the authors chose to utilize a Mitsunobu approach to generate sulfide **202** with a slight decrease in ee to 81% and 39% overall yield. Reaction of α-mercoptoacid **202** with MeSCN in refluxing toluene and treatment of the resulting 2-thiothiazolone with *S*-(*exo*)-2-aminonorbornane in methanol furnished AMG 221 (**203**) in 45-47% yield over two steps as a 9:1 mixture of C-5 epimers. In a second route, the enantioenriched cyanohydrin **201** was also employed as chiral starting material, but with net retention of configuration featuring a Vilsmeier–Haack reaction followed by treatment with enantiopure thiourea under basic conditions to afford **203** as a mixture of epimers in a 84:16 ratio.

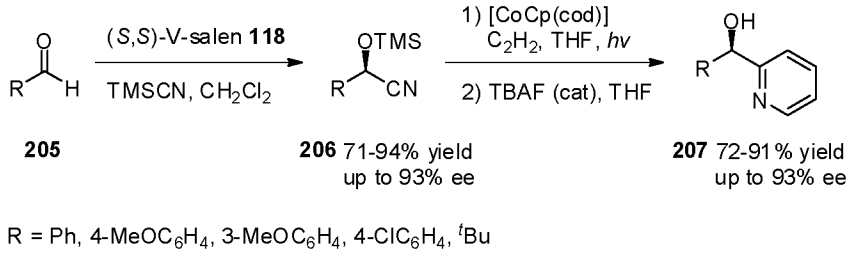
Scheme 1.43 *Two asymmetric syntheses of AMG-221 (**203**).*



1.4 Miscellaneous applications

Chiral cyanohydrins in combination with ethyne were subjected to a light-promoted cobalt(I)-catalyzed [2+2+2]-cyclotrimerization as was recently reported by the group of Hapke (Scheme 1.44).[63] They presented a novel two-step catalytic approach for the enantioselective synthesis of pyridyl alcohols using cyanohydrins as precursors. Using the chiral vanadium(IV)-salen complex (*S*,*S*)-**118** in combination with TMSCN, *O*-trimethylsilyl-protected cyanohydrins **206** were synthesized in high yield and ee. Applying the chiral cyanohydrins **206** in the presence of ethyne and the cobalt(I) catalyst to the photochemical cyclotrimerization reaction afforded the desired pyridyl alcohols **207** without racemization. After recrystallization, the products were isolated in enantiopure form. In contrast, the corresponding acetate cyanohydrins gave only low yields in the cyclotrimerization process.

Scheme 1.44 *Asymmetric synthesis of pyridyl alcohols via [2+2+2]-cyclotrimerization.*



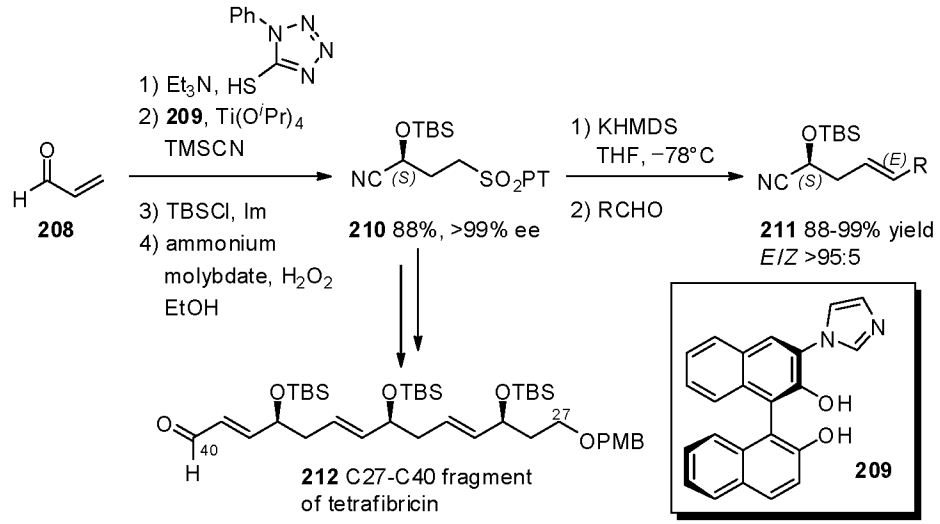
205 **206** 71-94% yield, up to 93% ee **207** 72-91 % yield, up to 93% ee

R = Ph, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-ClC_6H_4, ^{t}Bu

Friestad *et al.* designed a novel stereochemically controlled approach for the synthesis of 1,5-polyols based on a modified Julia–Kocienski olefination for carbon–carbon construction using configuration-encoded building blocks.[64] By selection of the proper stereogenic module during each stage of the iterative coupling sequence, (un)saturated 1,5-polyols could be created bearing all possible configurational permutations independent from the coupling chemistry. During the development of a reliable method, the investigators searched for a functional equivalent for the aldehyde being orthogonal to both *O*-silylation and olefination. They finally identified the nitrile moiety of a cyanohydrin as the best option for a masked aldehyde. As starting point, preparation of the α-silyloxy-γ-sulfononitrile **210** commenced with conjugate addition of PTSH to acrolein (**208**), followed by asymmetric cyanosilylation using 10 mol% of a chiral BINOL derivative **209** and $Ti(O^iPr)_4$ furnishing after TBS-protection the resulting cyanohydrin in 83–88% ee (Scheme 1.45). Sulfur-oxidation and recrystallization finally led to enantiopure sulfone **210** in 88% yield over four steps. Subjection of **210** to Julia–Kocienski olefination using various aldehydes smoothly provided the products **211** in excellent *E/Z*-selectivity (ratios ranging from 95:5 to >98:2) and yields up to 99%.

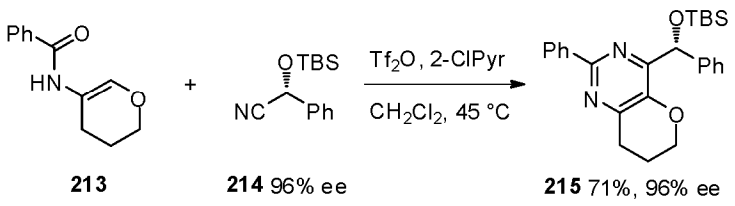
Application of the developed strategy proceeded through the synthesis of the C27–C40 fragment of tetrafibricin (**212**), a nonpeptide fibrinogen receptor antagonist, which was prepared in five steps in 42% overall yield using **210** as the recurring unit.

Scheme 1.45 *Novel stereoselective approach to 1,5-polyols.*



In a research project on the direct synthesis of substituted pyrimidines and quinazolines, researchers condensed the protected amide **213** with mandelonitrile **214** (Scheme 1.46).[65] In this single-step procedure, amide activation with Tf_2O in the presence of 2-chloropyridine, followed by addition of the (*R*)-mandelonitrile **214** to the activated amide derivative and cyclization, gave the desired azaheterocycle **215** under mild heating and without loss of optical activity.

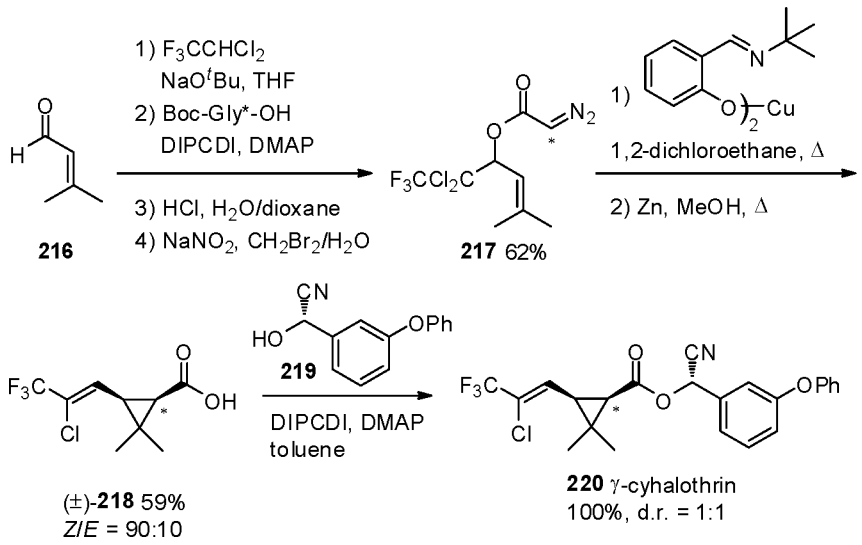
Scheme 1.46 *One-step synthesis of pyrimidine 215.*



As part of a research program on synthetic insecticides, researchers from Dow AgroSciences developed a high yielding radiochemical synthesis of γ–cyhalothrin (**220**) (Scheme 1.47).[66] Incorporation of a carbon-14 label in the cyclopropyl ring moiety was accomplished starting from readily available ^{14}C–labeled Boc-protected glycine (* = ^{14}C). Deprotection and treatment of the amine salt with sodium nitrite gave the diazoester **217**, which served as a key building block in the intramolecular cyclopropanation reaction. With

the aid of a homogeneous copper catalyst in refluxing 1,2-dichloroethane, the resulting bicyclic lactone was obtained which was then transformed into the desired cyclopropanecarboxylic acid **218** *via* zinc-mediated β–elimination of the lactone. The final stage of the synthesis was completed by recrystallization affording pure, but racemic *Z*-olefin isomer **218** (*Z*/*E* ratio >98%) which was then coupled with optically active cyanohydrin **219** (>99% ee) followed by separation of the 1:1 mixture of diastereoisomers.

Scheme 1.47 *Total synthesis of radiolabeled γ–cyhalothrin-1-*^{14}*C.*



1.5 Purpose and outline of the thesis

This thesis details our efforts and research on the development of novel synthetic methodology for the synthesis of biologically relevant functionalized heterocyclic compounds. Facile and efficient access to these scaffolds – preferentially in enantiomerically pure form – would provide a wide array of synthetic opportunities which are of relevance for the fields of organic chemistry, medicinal chemistry, and materials science. The starting materials in these investigations are enantiopure cyanohydrins, which are readily accessible in both enantiomeric forms *via* chemoenzymatic HNL-mediated hydrocyanide addition as has been previously developed in collaboration with DSM Research (Geleen, The Netherlands).

In this chapter, an overview has been given of recent synthetic applications of enantiopure cyanohydrins illustrating that these compounds have been broadly recognized as versatile building blocks.

The chemoenzymatic synthesis of *trans*-substituted aziridines is discussed in Chapter 2. A new method for the preparation of these compounds in high enantiomeric purity, based on a one-pot Grignard addition–reduction sequence, Cu^{II}-catalyzed diazotransfer, and reductive cyclization is described.

In Chapter 3, a novel approach for the synthesis of 4-hydroxy-2-pyrrolidines involving Au-catalyzed 5-*endo*-dig cyclization of aryl-substituted acetylenic amino alcohols is highlighted.

Inspired by the synthetic methodologies explored in the previous chapters, Chapter 4 discloses two attempts to synthesize a potent antitumor phenanthroindolizidine alkaloid using a chemoenzymatic approach. A third route details an attempt to synthesize the natural product *via* stereocontrolled acetylide addition reaction on Boc-(*S*)-prolinal.

Finally, Chapter 5 details the chemoenzymatic diastereoselective synthesis of both *cis*- and *trans*-2,5-disubstituted morpholines *via* a tandem reduction–transimination–reduction sequence and reductive radical detosylation.

1.6 References and notes

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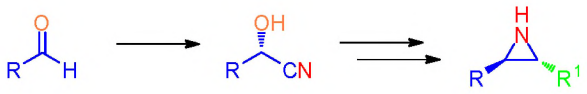
(66) Johnson, P. L. *J. Label Comp. Radiopharm.* **2007**, *50*, 47–53.

Chapter 2

Enantioselective Chemoenzymatic Synthesis of *trans*-Aziridines



A straightforward five-step procedure for the synthesis of enantiomerically pure 2,3-disubstituted *trans*-aziridines has been developed starting from commercially available aldehydes. Hydroxynitrile lyase-mediated cyanohydrin formation provided cyanohydrins in excellent enantioselectivities and good yields. Subsequent formation of diastereomerically pure *anti*-amino alcohols *via* a one-pot Grignard addition-reduction sequence, Cu^{II}-catalyzed diazotransfer, and triphenylphosphine-mediated reductive cyclization provided the corresponding *trans*-aziridines in good yields and excellent diastereoselectivities.

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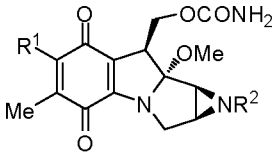
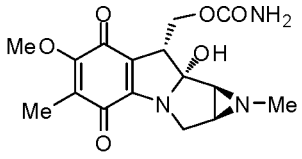
2.1 Introduction

Since the first synthesis by Gabriel in 1888,[1] aziridines have gained increasing interest in organic synthesis and medicinal chemistry.[2] Aziridines are highly reactive, but nevertheless occur in several natural products exhibiting potent biological activity. For instance, mitomycins A, B and C (**1**–**3**), together with porfiromycin **4** and mitiromycin **5**, represent an important class of naturally occurring *mitosanes*, first isolated from soil extracts of *Streptomyces versticillatus* (Figure 2.1).[3] These mitosanes[4] display both antibiotic and antitumor activity, the latter resulting from their ability to cross-link DNA. Structure-activity relationships[5] have identified the aziridine ring as being essential for such anti-tumor activity and extensive research has concentrated on synthesizing derivatives of these natural products with increased potency.[6]

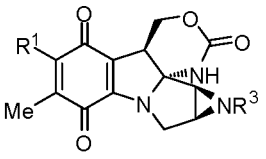
Figure 2.1 *Naturally occurring biologically active mitosanes.*



1 R^1 = OMe, R^2 = H; mitomycin A
3 R^1 = NH_2, R^2 = H; mitomycin C
4 R^1 = NH_2, R^2 = Me; porfiromycin



2 mitomycin B



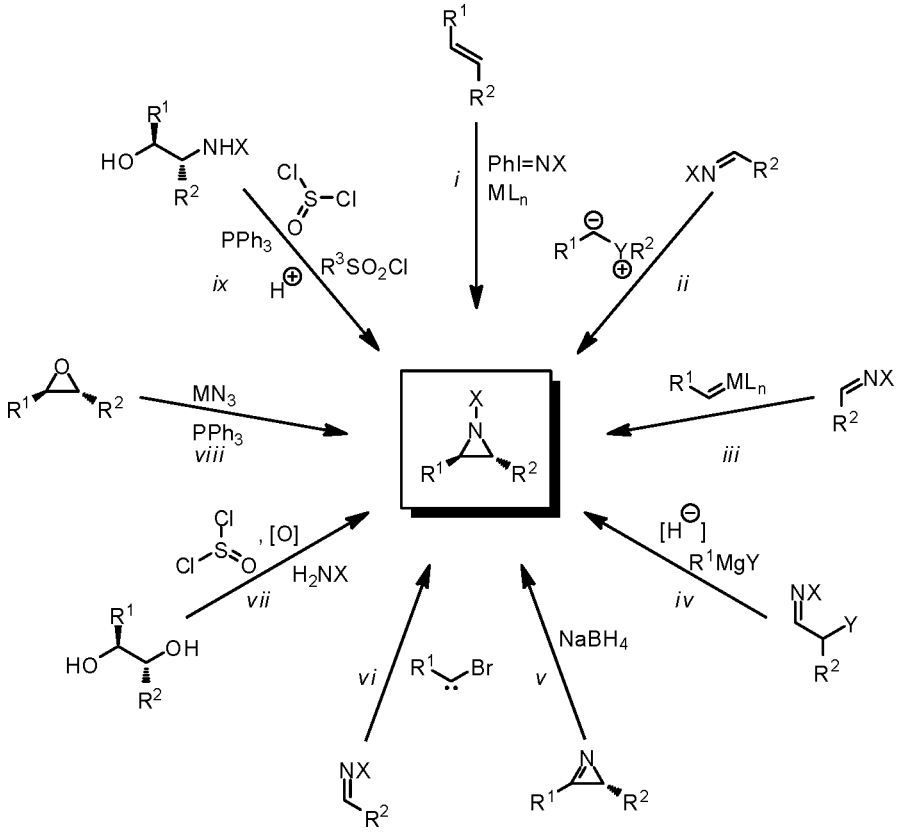
5 mitiromycin

The ability of aziridines to undergo regio- and stereoselective ring opening reactions, as well as ring expansions, provides direct access to various structural motifs and renders them attractive building blocks in organic synthesis. They have been applied in the total synthesis of natural products including alkaloids,[7] amino sugars,[8] amino acids[9] and lactam antibiotics such as (+)-thienamycin.[10] Other applications are found in asymmetric synthesis, where chiral aziridines have been utilized both as ligands and auxiliaries. Amongst these reactions are the asymmetric dihydroxylation of alkenes[11] and the enantioselective addition of dialkylzinc to various aliphatic and aromatic aldehydes.[12]

As a consequence, the development of efficient synthetic routes to aziridines has been an important subject of investigation over the past decades. Two of the most fundamental pathways involve (*i*) the metal-catalyzed addition of nitrenes to alkenes[13] and (*ii*) the addition of ylides to imines (Scheme 2.1).[14] Although frequently applied in the past, both methods lack

full stereocontrol over the outcome of the reaction and often require harsh conditions or the use of expensive catalysts. Other known methods for the synthesis of aziridines include (*iii*) addition of metal carbenoids to imines,[15] addition across α-halogenated imines,[16] (*v*) addition across azirines[17] and (*vi*) addition of carbenes to imines.[18] Furthermore, alkenes can readily be transformed into aziridines *via* (*vii*) cyclic sulfates, obtained from asymmetric dihydroxylation products and *via* (*viii*) epoxides, generated by application of the Sharpless asymmetric epoxidation.[19] However, the oldest and conceptually perhaps most obvious synthesis of aziridines utilizes (*ix*) 1,2-amino alcohols as precursors. In 1935, Wenker already demonstrated that addition of sulfuric acid to amino alcohols at elevated temperatures can yield enantiopure aziridines.[20] Direct ring closure of amino alcohols to provide aziridines is known to be difficult, and previous reports show only moderate yields.[21] Better results are obtained when the hydroxyl group is converted into a powerful leaving group, thus inducing an intramolecular displacement reaction. Several methods are described and extensive investigations of this reaction showed that aziridines can be isolated in high yield and stereoselectivity.[22]

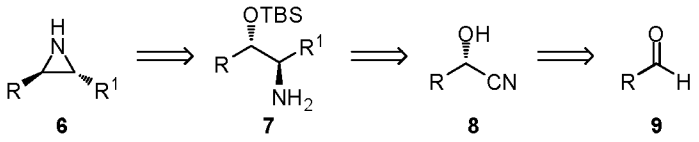
Scheme 2.1 *Overview of synthetic methodologies toward aziridines.*



2.2 Retrosynthetic strategy

Inspired by these examples and the relevance of the molecules we set out to investigate a new and readily applicable concise pathway for the synthesis of enantiomerically pure *trans*-aziridines (**6**). Our approach is outlined retrosynthetically in Scheme 2.2. We envisioned that the aziridine skeleton could arise *via* a direct closure of the aforementioned 1,2-amino alcohols (**7**), which would occur in a stereospecific manner. Furthermore, we hypothesized that optically active cyanohydrins (**8**) could be used as strategic synthons for the synthesis of the amino alcohols (**7**), exploiting the electrophilicity of the cyano group toward stereoselective addition of organometallic reagents. Finally, chemoenzymatic cyanohydrin formation was envisioned to provide these precursors in high ee using aldehydes (**9**) as substrates.

Scheme 2.2 *Retrosynthetic route to aziridines.*



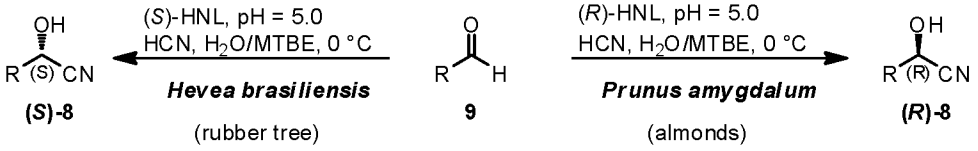
2.3 Chemoenzymatic asymmetric cyanohydrin formation

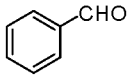
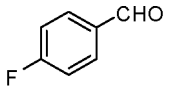
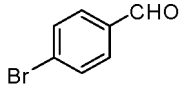
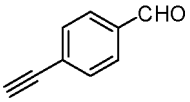
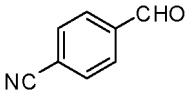
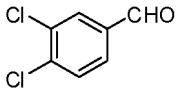
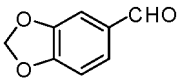
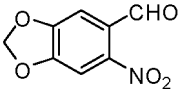
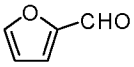
Inspired by previous work from the group of Effenberger[23] and due to our own general interest in the synthesis and application of chiral cyanohydrins,[24] the first step in our envisioned route was realized *via* hydroxynitrile lyase (HNL)-mediated cyanohydrin formation. Hydroxynitrile lyases are designed by nature to convert cyanohydrins into the corresponding aldehydes and hydrogen cyanide, which is used by some plants as a defense mechanism. Since their first application over a century ago,[25] HNLs have become more and more relevant biocatalysts for technical applications. By using a two-phase system of water, an immiscible organic solvent like methyl *tert*-butyl ether (MTBE), and a large excess of HCN, the equilibria can be efficiently directed to the cyanohydrin.[26]

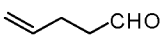
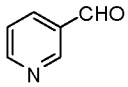
In the past, considerable effort has been spent to determine the substrate specificity of the enzymes. This specificity is known to be relatively wide, including both saturated and unsaturated aliphatic and aromatic aldehydes, heteroaromatic aldehydes, as well as aliphatic methyl ketones, albeit varying with different sources of HNL. In case of aliphatic aldehydes, it is known that longer chain lengths (> C_6) are usually not accepted. To have more insight

and to enlarge the scope of the HNL reaction, it was decided to first screen a series of eleven interesting aldehydes on substrate acceptance using the (*R*)-selective HNL from *Prunus amygdalus* (*Pa*HNL) and the (*S*)-selective HNL from *Hevea brasiliensis* (*Hb*HNL) as catalysts for conversion into the corresponding hydroxynitriles **8** (Table 2.1). The chemoenzymatic reactions were carried out under common HNL reaction conditions in a 1:1 buffer/MTBE mixture (pH 5) using 10 equiv of KCN at 0 °C. Conversions are reported on basis of HPLC measurements of the crude reaction products.

Table 2.1 *Screening of substrates for HNL-mediated cyanohydrin formation.*



entry	aldehyde	(*S*)-HNL		(*R*)-HNL	
		conversion (%)[a]	ee (%)[a]	conversion (%)[a]	ee (%)[a]
1		>99	>99	>99	>99
2		84	75	>99	93
3		>99	>99	>99	>99
4		–[b]	–[b]	>99	>99
5		87	54	>99	>99
6		95	90	93	>99
7		>99	>99	>99	>99
8		47	69	84	20
9		>99	>99	>99	>99

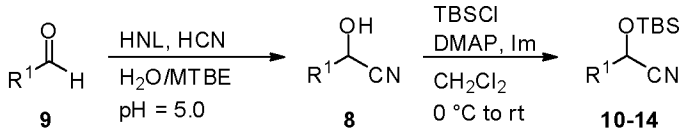
10		>99	>99	>99	>99
11		–[c]	–[c]	–[c]	–[c]

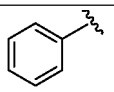
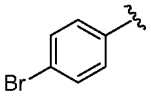
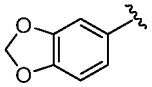
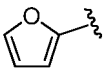
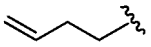
[a] Conversion and ee were determined by chiral HPLC using *i*PrOH:hexane, 20:80. [b] No reaction observed. [c] No product could be isolated.

As can been seen from Table 2.1, the (*R*)-selective HNL gives in nearly all cases excellent ee's and high conversions. On the other hand, subjection of some of the substrates to (*S*)-HNL is attended with lower conversions and moderate ee's. In entries 2 and 5, the aldehydes were converted rather slowly and, due to the longer reaction time needed, the non-enzymatic reaction had become more competitive, resulting in a lower ee and conversion. *p*-Ethynylbenzaldehyde turned out also to be not a suitable substrate for this enzyme and was not accepted at all, while (*R*)-HNL converts the aldehyde smoothly and in high ee (entry 4). In entry 8, usage of both enzymes led to low conversions and optical purities. However, in this case not only electronic interactions, but also steric effects of the *ortho*-substituent (nitro group) probably play a more decisive role. It is known that *ortho*-substituted substrates perform poorly in the chemoenzymatic synthesis of chiral cyanohydrins, resulting in low yields, TOF values, and/or low ee's.[27] Unfortunately, in entry 11 no product was detected at all. Attempts to isolate this cyanohydrin from the water layer also failed.

On the basis of this screening, we selected five different aldehydes for synthetic applications (Table 2.2). By using both (*R*)- and (*S*)-selective HNL as catalysts the corresponding hydroxynitriles **8** were obtained as crude products after filtration and extraction. Subsequent protection of the hydroxyl group (TBSCl, DMAP, imidazole) to prevent racemization and regeneration of the aldehyde, provided cyanohydrins **10**–**14** in good to high yield and excellent enantiomeric excess (Table 2.2).

Table 2.2 *HNL-mediated cyanohydrin formation and protection.*



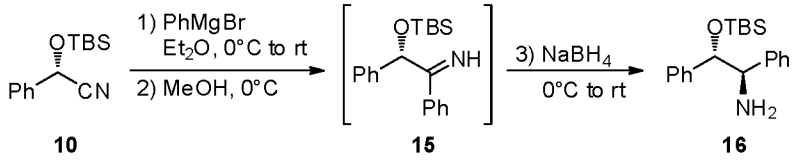
entry	R^1	enzyme	product	yield (%)[a]	ee (%)	config.
1		(*S*)-HNL	**10**	90	>99[b]	(*S*)
2		(*R*)-HNL	**11**	79	>99[c]	(*R*)
3		(*R*)-HNL	**12**	81	>99[b]	(*R*)
4		(*R*)-HNL	**13**	70	>99[c]	(*S*)[e]
5		(*R*)-HNL	**14**	67	>99[d]	(*R*)

[a] Isolated yield after chromatography. [b] Determined by GC analysis. [c] Determined by HPLC analysis. [d] Determined by derivatization with Mosher's acid chloride and comparison with the diastereomeric esters prepared from their racemic counterparts. [e] The stereochemical arrangement is as expected for the (*R*)-HNL: however, due to priority changes following the Cahn-Ingold-Prelog rules, the product has the (*S*)-configuration.

2.4 Stereocontrolled imine reduction

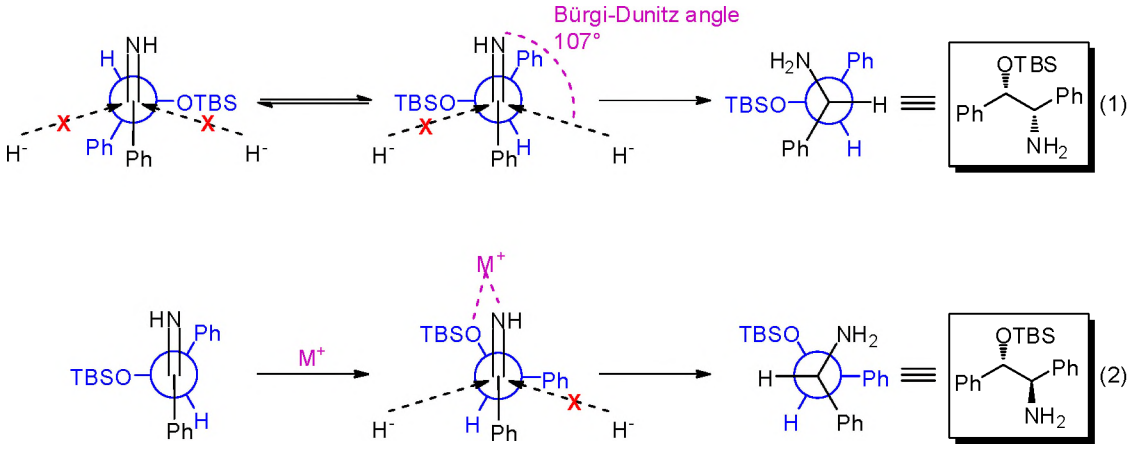
In order to introduce the second stereogenic center, we used an elegant method developed by Brussee *et al.*,[28] which relied on a tandem Grignard addition-$NaBH_4$ reduction sequence providing the desired products in high yield and excellent diastereoselectivity. Thus, addition of phenylmagnesium bromide to cyanohydrin **10** in diethyl ether at 0 °C smoothly afforded the metallo imine, as was monitored by mass analysis. Dry methanol was added to destroy the excess of Grignard reagent and to protonate the primary imine anion intermediate (Scheme 2.3). *In situ* reduction by adding an excess of $NaBH_4$ took place in a diastereoselective fashion according to Cram's chelation model,[29] affording **16** in 92% yield with excellent diastereoselectivity (dr 99%, entry 1, Table 2.3).

Scheme 2.3 *Tandem Grignard addition-$NaBH_4$ reduction sequence.*



A stereochemical explanation is given in Scheme 2.4 where according to the Felkin–Anh model[30] the possible trajectories of the two thermodynamically most stable conformers of the intermediate imines are shown. The hydride will attack along the less hindered pathway, along the Bürgi–Dunitz angle,[31] affording the *syn*-diastereoisomer (equation 1, Scheme 2.4). When chelation is possible, *e.g.* in the presence of a Grignard reagent, the magnesium will chelate between the imine and oxygen, changing the conformation of the intermediate imine. Attack is still along the less hindered pathway, but the stereochemical outcome is reversed, resulting in the *anti*-diastereoisomer (equation 2, Scheme 2.4).

Scheme 2.4 *Stereoselective imine reduction.*



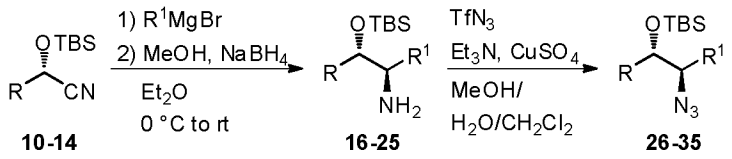
Pleased with these results, we applied the one-pot reaction sequence on cyanohydrins **10**–**14** by using various Grignard reagents. Gratifyingly, the desired *anti*-amino alcohols **16**–**25** could be isolated in reasonable to good yields (Table 2.3). In case of entry 3, the addition of 3-chlorophenylmagnesium bromide proceeded much slower and produced only 21% of alcohol **18**. Prolonged stirring or other attempts to improve the yield led to considerable side product formation. It seems conceivable that steric interactions play an important role in this reaction. Additionally, we were pleased to find that in all cases the dr of the reaction sequence was

>95%, except for entry 10, which showed a significantly lower dr of 72%. This discrepancy is presumably caused by the decreased size of the butenyl side chain of the cyanohydrin, resulting in a smaller difference between both diastereofaces. Synthetic efforts to react cyanohydrin **14** with aliphatic Grignard reagents provided the desired amino alcohols in rather poor dr. For this reason we decided to focus on the synthesis of the aromatic amino alcohols.

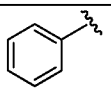
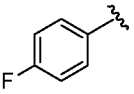
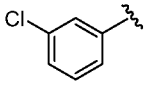
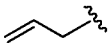
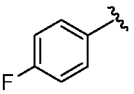
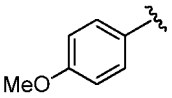
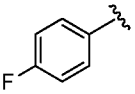
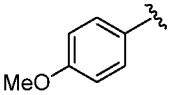
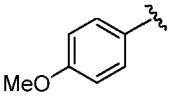
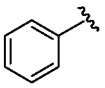
2.5 Aziridine formation

In a first attempt to cyclize the amino alcohols to the corresponding aziridines, simultaneous nosylation of both the alcohol and amino functionality was investigated. Various reaction conditions were explored, but unfortunately this approach afforded only mixtures of *N*-sulfonylated product with small amounts of the desired precursor. With this precursor in hand, however, we continued with the base-catalyzed cyclization. Much to our surprise, all cyclization efforts failed, even after prolonged reaction times. Heating of the reaction mixture up to 50 °C to force the ring closure merely led to formation of side products. Considering these results, we concluded that direct ring closure of the free amino alcohol using Mitsunobu-type conditions might be more successful. Subjection of the amino alcohol to PPh_3 in combination with either DEAD or DIAD in various solvents, however, did not result in any reaction despite some literature precedent on similar substrates.[22a,32] A modified synthetic route involving protection of the nitrogen atom to enhance the Mitsunobu reaction would be less attractive since this requires an additional deprotection step to afford the unprotected aziridine. Consequently, an alternative approach was conceptualized involving the introduction of an azide functionality. The chosen conditions for a Cu^{II}-catalyzed diazotransfer reaction were based on comparison between two different literature procedures, namely with imidazole-1-sulfonyl azide[33] and triflic azide[34] as reagents. Because the latter reaction gave the highest yield (near quantitative) for the conversion of **16** to the corresponding azido alcohol **26**, we decided to conduct all diazotransfer reactions under these conditions. Thus, subjection of the amino alcohols **16**–**25** under the aforementioned conditions, afforded the azido alcohols **26**–**35** in good yields (64–99%, Table 2.3).

Table 2.3 *Grignard addition, reduction and diazotransfer.*



10-14 **16-25** **26-35**

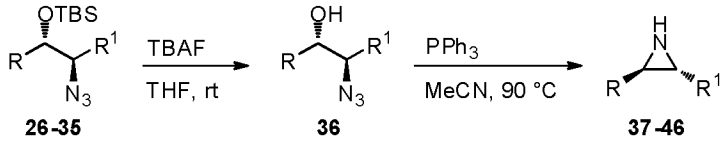
entry	s.m.	R^1	amino alcohol	yield (%)[a]/ dr (%)[b]	azido alcohol	yield (%)[a]	config.
1	**10**		**16**	92/99	**26**	99	(*S*,*R*)
2	**10**		**17**	70/99	**27**	93	(*S*,*R*)
3	**10**		**18**	21/99	**28**	99	(*S*,*R*)
4	**10**		**19**	64/95	**29**	91	(*S*,*R*)
5	**11**		**20**	51/99	**30**	87	(*R*,*S*)
6	**11**		**21**	49/99	**31**	76	(*R*,*S*)
7	**13**		**22**	52/99	**32**	66	(*S*,*S*)
8	**13**		**23**	53/99	**33**	64	(*S*,*S*)
9	**12**		**24**	91/99	**34**	90	(*R*,*S*)
10	**14**		**25**	52/72	**35**	76	(*R*,*S*)

[a] Isolated yield after chromatography. [b] Determined by ^{1}H NMR analysis of the crude product.

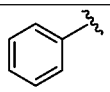
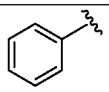
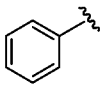
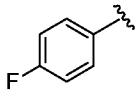
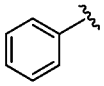
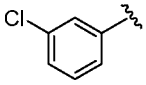
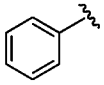
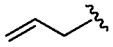
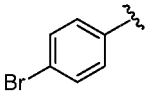
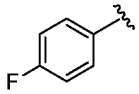
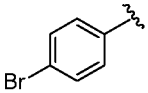
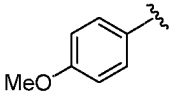
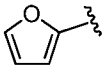
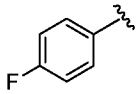
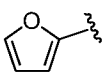
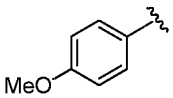
With the *anti*-azido alcohols in hand, the stage was set for the synthesis of the *trans*-aziridines (Table 2.4). Deprotection with TBAF in THF resulted in clean conversion into the corresponding free azido alcohols, which upon a simple extraction without further purification could be used in a phosphine-mediated Staudinger-type ring closure.[35]

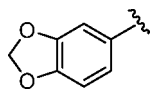
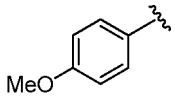
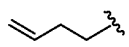
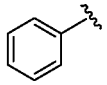
Performing the cyclization in THF or DMF at elevated temperatures (70–90 °C) in combination with trimethylphosphine initially led to poor conversion into the desired *trans*-aziridine. A more rewarding result was obtained by stirring the *anti*-azido alcohols in the presence of triphenylphosphine in refluxing acetonitrile. Much to our satisfaction, the aziridines **37**–**42** and **45**–**46** could be isolated in moderate to good yields (46–89%, Table 2.5). In an attempt to avoid the tedious purification from triphenylphosphine oxide, polymer-bound triphenylphosphine was also used. As anticipated, this decreased the reaction rate dramatically, but did not improve the yield.

Table 2.5 *Desilylation and ring closure.*



26-35 **36** **37-46**

entry	s.m.	R	R^1	product	Yield (%)[a]/ dr (%)[b]	config.
1	**26**			**37**	60/99	(*R*,*R*)
2	**27**			**38**	47/99	(*R*,*R*)
3	**28**			**39**	89/99	(*R*,*R*)
4	**29**			**40**	51/99	(*R*,*R*)
5	**30**			**41**	73/99	(*S*,*S*)
6	**31**			**42**	53/99	(*S*,*S*)
7	**32**			**43**	–[c]	–
8	**33**			**44**	–[c]	–

9	**34**			**45**	54/99	(*S*,*S*)
10	**35**			**46**	46/99	(*S*,*S*)

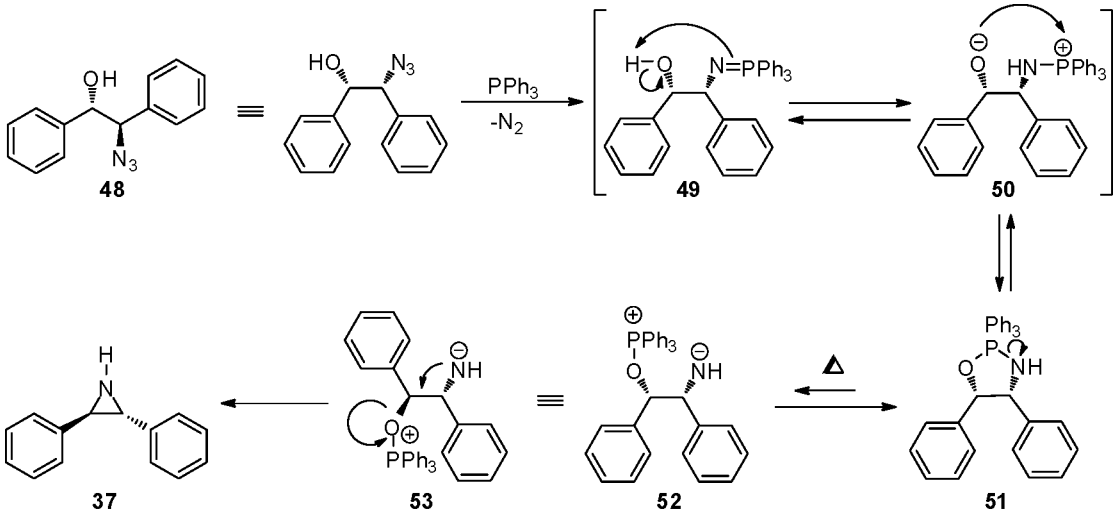
[a] Isolated yield after chromatography. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Product decomposed during reaction.

Unfortunately, in case of entries 7 and 8 no product could be isolated. Although mass spectrometry of the reaction mixture showed formation of the intermediate oxazaphospholidine and a product with the expected mass, we were unable to isolate the desired aziridines. A suitable mechanistic explanation is lacking, although a partial answer may lie in the electron-donating capacity of the furanyl substituent.

Furthermore, we proved by using chiral HPLC analysis of acetylated **37** that no (partial) racemization had taken place during the whole sequence. Optical rotation measurements were compared to literature values and proved the formation of the *trans*-substituted aziridine **47**.[36]

A mechanistic rationale for this reaction is provided in Scheme 2.5. The first part of this particular sequence revolves around the reaction of the hydroxyazide with trialkyl- or triarylphosphine, leading to the iminophosphorane **49** through nucleophilic addition of the phosphine at the terminal nitrogen atom of the azide and expulsion of nitrogen. Subsequently, the oxazaphospholidine **51** is formed, which upon thermal activation cyclizes with inversion of configuration to yield the aziridine **37**.

Scheme 2.5 *Mechanism of the phosphine-mediated Staudinger-type ring closure.*



2.6 Conclusions

In summary, a novel and straightforward procedure has been developed that allows for the synthesis of unprotected *trans*-aziridines starting from commercially available aldehydes. The key step in this relatively mild sequence involves chemoenzymatic enantioselective HNL-mediated cyanohydrin formation. We also demonstrated that the corresponding *anti*-amino alcohols could be synthesized in good yields and excellent diastereoselectivities. The last two steps in the sequence, diazotransfer and phosphine-mediated ring closure, produced the target aziridines in high yield and enantiomeric purity.

2.7 Acknowledgments

Matthijs C. M. van Oers and Niek J. Vermue are gratefully acknowledged for their contribution to this chapter. DSM Pharma Chemicals (Geleen, the Netherlands) is kindly acknowledged for providing the HNL enzymes.

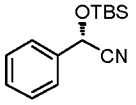
2.8 Experimental section

General information

All reactions were performed under an argon atmosphere, unless stated otherwise. Solvents were purified from water and oxygen (MBraun SPS-800 solvent purification system) prior to use. Et_3N was distilled and stored over KOH. All other chemicals were purchased from commercial suppliers and were used without further purification, unless stated otherwise. Reactions were followed, and R_f values are obtained using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated eluens and compounds were detected with UV-light and/or by charring at ca. 150 °C after dipping into a solution of potassium permanganate, anisaldehyde, or ninhydrin. Column or flash chromatography was carried out using ACROS silica gel (0.035-0.070 mm, pore diameter ca. 6 mm). IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. High-resolution mass spectra were recorded on a JEOL AccuTOF (ESI) or a MAT900 (EI, CI, and ESI). Low-resolution ESI mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max Ion Trap mass spectrometer. Melting points were analyzed with a Büchi melting point B-545 and are not corrected. High Performance Liquid Chromatography (HPLC) measurements were conducted on a HPLC apparatus equipped with a Chiralpak AD-H column (dimensions: 250 × 4.6 mm) and peaks were detected using a UV-detector. Gas chromatography (GC) was performed on a Hewlett Packard 5890, containing a HP1 column (dimensions: 25 m × 0.32 mm × 0.17 μm), FID detection, and

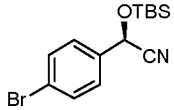
equipped with a HP3393A integrator. GC measurements were conducted on a GC apparatus equipped with a GAMMA DEX 120 column (dimensions: 30 m × 0.25 mm, 0.25 μm film) and peaks were detected using a UV-detector. NMR spectra were recorded at 298 K on a Bruker DMX 300 (300 MHz) and a Varian 400 (400 MHz) spectrometer in the solvent indicated. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm), or CHD_2OD (3.31 ppm) as internal standard for ^{1}H-NMR; and $CDCl_3$ (77.16 ppm), or CD_3OD (49.00 ppm) as internal standard for ^{13}C-NMR.[37] Coupling constants are reported as *J* values in hertz (Hz). The gene encoding for (*S*)-HNL, originating from the rubber tree *Hevea brasiliensis*, was cloned and efficiently expressed in the yeast strain *Pichia pastoris* as an intracellular protein; the enzyme preparation was obtained by homogenization (French press) of the cells, removal of insolubles by filtration, and subsequent concentration of the clear filtrate using ultrafiltration/diafiltration.[38] The wild type gene encoding for (*R*)-HNL, originating from bitter almonds (*Prunus amygdalus*), was cloned and efficiently expressed in the yeast strain *P. pastoris*. The enzyme was secreted from the cells (*P. pastoris*), and was obtained from cell free supernatant by concentration using ultrafiltration/diafiltration.[39] The crude lysates (cell–free extracts) containing (*R*)-HNL and (*S*)-HNL were kindly provided by DSM Research (Geleen, The Netherlands).

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylacetonitrile (10)



A solution of benzaldehyde (500 mg, 4.71 mmol) in MTBE (40 mL) was added to a cooled (0 °C) solution of KCN (3.07 g, 47.1 mmol, 10 equiv) in citrate buffer (40 mL, pH = 5.0). After addition of (*S*)-HNL (800 μL) the reaction mixture was stirred at 0 °C for 1.5 h and quenched with 5 M HCl (5 mL), causing the enzyme to precipitate. The precipitate was filtrated over a glass funnel filled with cotton. The filtrate was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (15 mL) at 0 °C and TBSCl (781 mg, 5.18 mmol, 1.1 equiv), imidazole (641 mg, 9.42 mmol, 2.0 equiv, dissolved in 1 mL CH_2Cl_2) and DMAP (58 mg, 10 mol %) were added successively. The reaction mixture was stirred overnight at 0 °C. After diluting the reaction mixture with H_2O (15 mL) and Et_2O (15 mL), the organic layer was washed with H_2O (2 × 30 mL) and brine (2 × 30 mL). The resulting organic fraction was dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (EtOAc/heptane, 1:7→1:1) yielded compound **10** (1.05 g, 90%) as a colorless oil. R_f 0.65 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +16.8 (*c* 1.05, $CHCl_3$). {ref. $[\alpha]_D^{20}$ +17.5 (*c* 1.00, $CHCl_3$)}. e.e >99% (GC, isothermic, 120 °C); $R_{t,1}$ = 13.90 min (*S*), $R_{t,2}$ = 14.38 min (*R*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.38 (m, 5H), 5.53 (s, 1H), 0.95 (s, 9H), 0.24 (s, 3H), 0.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.5, 129.2, 128.9, 126.0, 119.3, 64.0, 25.5, 18.2, −5.1, −5.2. Data are in agreement with literature.[40]

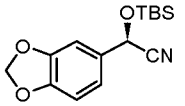
(*R*)-2-(4-Bromophenyl)-2-(*tert*-butyldimethylsilyloxy)acetonitrile (11)



Prepared as described above starting from *p*-bromobenzaldehyde (500 mg, 2.36 mmol) and (*R*)-HNL. Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **11** (608 mg, 79%) as a colorless oil. R_f 0.60 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +6.3 (*c* 1.16, CH_2Cl_2). e.e >99% (HPLC eluent hexane:ethanol = 98:2, flow 1.0 mL/min); $R_{t,1}$ = 4.38 min (*R*), $R_{t,2}$ = 5.09 min (*S*). IR (ATR): 2954, 2926, 2858, 1256, 1093, 841 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.57 (m, 2H), 7.45-7.40 (m, 2H), 5.46 (s, 1H), 0.94 (s, 9H), 0.23 (s, 3H), 0.16 (s, 3H). ^{13}C NMR

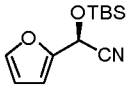
($CDCl_3$, 75 MHz): δ 135.7, 131.8, 127.9, 123.5, 118.9, 63.6, 25.7, 18.3, −4.9, −5.1. HRMS (EI) *m/z* calcd for $C_{14}H_{20}BrNOSi$ $(M)^+$: 327.0478, found: 327.0472.

(*R*)-2-(3,4-Methylenedioxylphenyl)-2-(*tert*-butyldimethylsilyloxy)acetonitrile (12)



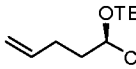
Prepared as described above starting from piperonal (500 mg, 3.33 mmol) and (*R*)-HNL. Column chromatography (EtOAc/heptane, 1:7→1:1) afforded **12** (671 mg, 70%) as a colorless oil. R_f 0.66 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +12.9 (*c* 1.41, CH_2Cl_2) {ref. $[\alpha]_D^{20}$ +17.0 (*c* 1.00, $CHCl_3$)} e.e. >99% (HPLC eluent hexane:isopropanol = 90:10, flow 1.0 mL/min); $R_{t,1}$ = 3.72 min (*S*), $R_{t,2}$ = 4.27 min (*R*). IR (ATR): 2954, 2928, 2894, 2868, 1489, 1249, 839 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.96 (d, *J* = 1.8 Hz, 1H), 6.91 (dd, *J* = 1.8, 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 5.40 (s, 1H), 0.93 (s, 9H), 0.22 (s, 3H), 0.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.5, 148.4, 130.6, 120.1, 119.4, 108.5, 106.9, 101.6, 63.9, 25.5, 18.3, −5.0, −5.1. HRMS (FAB) *m/z* calcd for $C_{15}H_{22}NO_3Si$ $(M+H)^+$: 292.1369, found: 292.1362. Data are in agreement with literature.[41]

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl)acetonitrile (13)



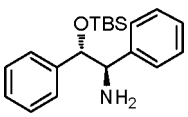
Prepared as described above starting from furfural (1.00 g, 10.4 mmol) and (*R*)-HNL. Column chromatography (EtOAc/heptane, 1:7→1:1) afforded **13** (906 mg, 81%) as a yellow oil. R_f 0.65 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +10.9 (*c* 1.11, CH_2Cl_2) {ref.[42] $[\alpha]_D^{20}$ +18.9 (*c* 5.00, $CHCl_3$)}. e.e. >99% (GC, isothermic, 120 °C); $R_{t,1}$ = 15.72 min (*R*), $R_{t,2}$ = 17.74 min (*S*). IR (ATR): 2954, 2933, 2859, 1256, 1087, 840 cm-1. 1H NMR (CDCl3, 400 MHz): δ 7.45 (dd, *J* = 0.8, 1.8 Hz, 1H), 6.53 (dd, *J* = 0.7, 3.3 Hz, 1H), 6.40 (dd, *J* = 1.9, 3.3 Hz, 1H), 5.55 (s, 1H), 0.91 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.5, 143.7, 117.2, 110.7, 109.4, 58.1, 25.4, 18.2, −5.3. HRMS (CI) *m/z* calcd for $C_{12}H_{20}NO_2Si$ $(M+H)^+$: 238.1263, found: 238.1266.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)hex-5-enenitrile (14)



Prepared as described above starting from 4-pentenal (700 mg, 8.32 mmol) and (*R*)-HNL. Column chromatography (EtOAc/heptane, 1:7→1:1) afforded **14** (1.26 g, 67%) as a colorless oil. R_f 0.72 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ +0.55 (*c* 1.17, CH_2Cl_2). e.e. >99% ((*R*)-Mosher acid). IR (ATR): 3075, 2954, 2846, 1460, 1170, 1013, 719 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.78 (ddt, *J* = 10.2, 16.9, 6.6 Hz, 1H), 5.11-5.03 (m, 2H), 4.44 (t, *J* = 6.6 Hz, 1H), 2.27-2.21 (m, 2H), 1.92-1.87 (m, 2H), 0.91(s, 9H), 0.19 (s, 3H), 0.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.4, 120.1, 116.3. 61.3, 35.6, 28.7, 25.7, 18.2, −5.0, −5.2. HRMS (CI) *m/z* calcd for $C_{11}H_{23}OSi$ $(M-CN)^+$: 199.1518, found: 199.1518. Data are in agreement with literature.[43]

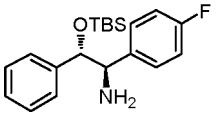
(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,2-diphenylethanamine (16)



A solution of cyanohydrin **10** (1.00 g, 4.04 mmol) in dry Et_2O (30 mL) was cooled to 0 °C and phenylmagnesium bromide (4.04 mL of a 3.0 M solution in Et_2O, 12.1 mmol, 3.0 equiv) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h, after which MeOH (30 mL) and $NaBH_4$ (611 mg, 16.2 mmol, 4 equiv) were added. After 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$ (60 mL) and the product was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (EtOAc/heptane, 1:7→1:1) afforded pure **16** (1.19 g, 90%) as a colorless oil. R_f 0.41 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +31.6 (*c* 1.07, CH_2Cl_2). IR (ATR): 2953, 2926, 2855, 1093, 836, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.19 (m, 10H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.02 (d, *J* = 6.5 Hz, 1H), 1.37 (br s, 1H), 0.75 (s, 9H), −0.25 (s,

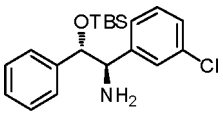
3H), −0.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.7, 142.0, 127.9, 127.8, 127.4, 127.2, 127.1, 80.2, 62.9, 29.7, 25.7, 18.0, −5.0, −5.7 HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NOSi$ $(M+H)^+$: 328.2097, found: 328.2103.

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4-fluorophenyl)-2-phenylethanamine (17)



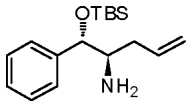
Prepared as described above starting from cyanohydrin **10** (500 mg, 2.02 mmol) and *p*-fluorophenylmagnesium bromide (6.06 mL of a 1 M solution in THF, 6.06 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **17** (488 mg, 70%) as a yellowish oil. R_f 0.38 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +33.5 (*c* 1.27, CH_2Cl_2). IR (ATR): 2954, 2925, 2850, 1509, 1093, 836 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.16 (m, 7H), 7.00-6.92 (m, 2H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.00 (d, *J* = 6.5 Hz, 1H), 1.45 (br s, 1H), 0.75 (s, 9H), −0.24 (s, 3H), −0.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.6 (d, *J* = 244.7 Hz), 141.8, 138.3 (d, *J* = 2.6 Hz), 129.3 (d, *J* = 7.9 Hz), 127.9, 127.6, 127.1, 114.5 (d, *J* = 21.1 Hz), 80.0, 62.2, 25.6, 18.0, −5.0, −5.6. HRMS (ESI) m/z calcd for $C_{20}H_{29}FNOSi$ $(M+H)^+$: 346.2002, found: 346.1995.

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-(3-chlorophenyl)-2-phenylethanamine (18)



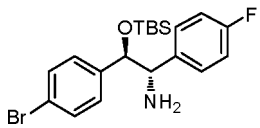
Prepared as described above starting from cyanohydrin **10** (300 mg, 1.21 mmol) and 3-chlorophenylmagnesium bromide (7.26 mL of a 0.5 M solution in THF, 3.63 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **18** (114 mg, 26%) as a yellowish oil. R_f 0.46 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +31.9 (*c* 1.60, CH_2Cl_2). IR (ATR): 2950, 2928, 2850, 1593, 1467, 1251, 1091, 835 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.12 (m, 9H), 4.56 (d, *J* = 6.7 Hz, 1H), 3.97 (d, *J* = 6.7 Hz, 1H), 0.75 (s, 9H), −0.26 (s, 3H), −0.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.1, 142.0, 133.8, 129.0, 128.3, 128.0, 127.7, 127.2, 127.1, 126.1, 80.2, 62.7, 25.8, 18.1, −4.9, −5.6. HRMS (ESI) *m/z* calcd for $C_{20}H_{29}ClNOSi$ $(M+H)^+$: 362.1707, found: 362.1703.

(1*S*,2*R*)-2-Amino-1-(*tert*-butyldimethylsilyloxy)-1-phenylpent-4-ene (19)



Prepared as described above starting from cyanohydrin **10** (250 mg, 1.01 mmol) and allylmagnesium bromide (3.03 mL of a 1 M solution in Et_2O, 3.03 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **19** (118 mg, 40%) as a yellowish oil. R_f 0.30 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +34.9 (*c* 0.97, CH_2Cl_2). IR (ATR): 2954, 2927, 2856, 1254, 1087, 1065, 837 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.17 (m, 5H), 5.76 (dddd, *J* = 6.1, 8.2, 10.2, 16.5 Hz, 1H), 5.09-5.01 (m, 2H), 4.43 (d, *J* = 5.9 Hz, 1H), 2.89 (ddd, *J* = 3.9, 5.7, 9.3 Hz, 1H), 2.43-2.33 (m, 1H), 1.93-1.85 (m, 1H), 0.84 (s, 9H), −0.01 (s, 3H), −0.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.1, 136.1, 127.9, 127.4, 127.0, 117.3, 78.7, 57.2, 37.4, 18.1, −4.6, −5.1. HRMS (ESI) *m/z* calcd for $C_{17}H_{30}NOSi$ $(M+H)^+$: 292.2097, found: 292.2085. Data are in agreement with literature.[44]

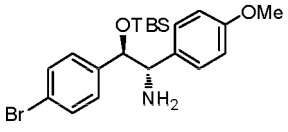
(1*S*,2*R*)-2-(4-Bromophenyl)-2-(*tert*-butyldimethylsilyloxy)-1-(4-fluorophenyl)ethanamine (20)



Prepared as described above starting from cyanohydrin **11** (150 mg, 0.46 mmol) and *p*-fluorophenylmagnesium bromide (1.38 mL of a 1 M solution in THF, 1.38 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **20** (99 mg, 51%) as a yellowish oil. R_f 0.43 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −27.2 (*c* 0.93, CH_2Cl_2). IR (ATR): 2958, 2931, 2890, 2858, 1508, 1223, 1085, 835, 777 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.37 (m, 2H), 7.21-7.17 (m, 2H), 7.06-7.03

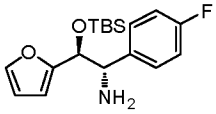
(m, 2H), 6.98-6.94 (m, 2H), 4.57 (d, J = 6.1 Hz, 1H), 3.98 (d, J = 6.1 Hz, 1H), 1.50 (br s, 1H), 0.77 (s, 9H), −0.21 (s, 3H), −0.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1 (d, J = 245.0 Hz), 140.7, 137.9, 131.0, 129.3 (d, J = 7.9 Hz), 128.8, 121.4, 114.6 (d, J = 21.1 Hz), 79.4, 62.0, 25.8, 18.0, −4.9, −5.5. HRMS (ESI) *m/z* calcd for $C_{20}H_{28}BrFNOSi$ $(M+H)^+$: 424.1108, found: 424.1103.

(1*S*,2*R*)-2-(4-Bromophenyl)-2-(*tert*-butyldimethylsilyloxy)-1-(4-methoxyphenyl)ethanamine (21)



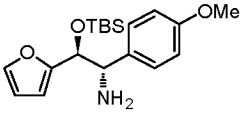
Prepared as described above starting from cyanohydrin **11** (116 mg, 0.36 mmol) and *p*-methoxyphenylmagnesium bromide (2.14 mL of a 0.5 M solution in THF, 1.08 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **21** (77 mg, 49%) as a yellowish oil. R_f 0.42 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −14.2 (*c* 1.00, CH_2Cl_2). IR (ATR): 2954, 2924, 2850, 1511, 1248, 1086, 835, 777 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.35 (m, 2H), 7.14-7.08 (m, 2H), 7.05-7.00 (m, 2H), 6.83-6.78 (m, 2H), 4.61 (d, J = 5.8 Hz, 1H), 3.96 (d, J = 4.6 Hz, 1H), 3.79 (s, 3H), 1.46 (br s, 1H), 0.78 (s, 9H), −0.18 (s, 3H), −0.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.8, 141.0, 134.3, 130.8, 128.8, 128.9, 121.2, 113.2, 79.4, 62.0, 55.3, 25.7, 18.0, −4.9, −5.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{31}BrNO_2Si$ $(M+H)^+$: 436.1307, found: 436.1301.

(1*S*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4-fluorophenyl)-2-(furan-2-yl)ethanamine (22)



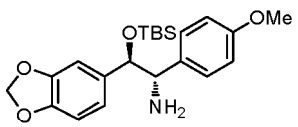
Prepared as described above starting from cyanohydrin **13** (200 mg, 0.84 mmol) and *p*-fluorophenylmagnesium bromide (2.53 mL of a 1 M solution in THF, 2.53 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **22** (138 mg, 49%) as a yellowish oil. R_f 0.37 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −42.1 (*c* 1.02, CH_2Cl_2). IR (ATR): 2953, 2928, 2856, 1509, 1225, 1091, 837, 778 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (dd, J = 0.8, 1.8 Hz, 1H), 7.31-7.27 (m, 2H), 7.01-6.95 (m, 2H), 6.32 (dd, J = 1.8, 3.2 Hz, 1H), 6.20 (dd, J = 0.4, 3.2 Hz, 1H), 4.59 (d, J = 7.2 Hz, 1H), 4.19 (d, J = 7.2 Hz, 1H), 1.51 (br s, 1H), 0.71 (s, 9H), −0.22 (s, 3H), −0.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.6 (d, J = 244.7 Hz), 154.2, 141.4, 137.9, 128.7 (d, J = 7.9 Hz), 114.2 (d, J = 21.2 Hz), 109.6, 107.6, 73.5, 59.6, 29.2, 17.9, −5.9, −6.1. HRMS (ESI) *m/z* calcd for $C_{18}H_{27}FNO_2Si$ $(M+H)^+$: 336.1795, found: 336.1779.

(1*S*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl)-1-(4-methoxyphenyl)ethanamine (23)



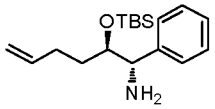
Prepared as described above starting from cyanohydrin **13** (200 mg, 0.84 mmol) and *p*-methoxyphenylmagnesium bromide (5.04 mL of a 0.5 M solution in THF, 2.52 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **23** (155 mg, 53%). R_f 0.38 (EtOAc/heptane, 1:1) as a yellowish oil. $[\alpha]_D^{20}$ −26.6 (*c* 1.01, CH_2Cl_2). IR (ATR): 2953, 2926, 2855, 1512, 1248, 1902, 835, 777 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (dd, J = 0.8, 1.8 Hz, 1H), 7.25-7.21 (m, 2H), 6.85-6.82 (m, 2H), 6.31 (dd, J = 1.8, 3.2 Hz, 1H), 6.20 (dd, J = 0.4, 3.2 Hz), 4.61 (d, J = 7.2 Hz, 1H), 4.16 (d, J = 7.1 Hz, 1H), 3.80 (s, 3H), 1.50 (br s, 1H), 0.72 (s, 9H), −0.22 (s, 3H), −0.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.8, 155.0, 141.7, 134.8, 128.6, 113.4, 110.1, 107.9, 74.1, 60.1, 55.3, 25.6, 18.0, −5.4, −5.6. HRMS (ESI) *m/z* calcd for $C_{19}H_{30}NO_3Si$ $(M+H)^+$: 348.1995, found: 348.1994.

(1*S*,2*R*)-2-(3,4-Methylenedioxylphenyl)-2-(*tert*-butyldimethylsilyloxy)-1-(4-methoxyphenyl)ethan amine (24)



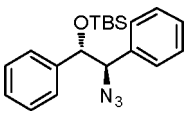
Prepared as described above starting from cyanohydrin **12** (150 mg, 0.52 mmol) and *p*-methoxyphenylmagnesium bromide (3.12 mL of a 0.5 M solution in THF, 1.56 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **24** (189 mg, 91%) as a yellowish oil. R_f 0.28 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −18.7 (*c* 0.44, CH_2Cl_2). IR (ATR): 2958, 2928, 2889, 2850, 1246, 1039, 835 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21-7.16 (m, 2H), 6.85-6.80 (m, 2H), 6.75 (s,1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.95 (d, *J* = 1.3 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 4.50 (d, *J* = 6.4 Hz, 1H), 3.91 (d, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 1.42 (br s, 1H), 0.75 (s, 9H), −0.24 (s, 3H), −0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 147.5, 146.9, 136.5, 135.1, 129.0, 120.8, 113.4, 107.6, 107.5, 101.0, 80.2, 62.4, 55.4, 25.9, 18.2, −4.7, −5.3. HRMS (ESI) *m/z* calcd for $C_{22}H_{32}NO_4Si$ $(M+H)^+$: 402.2101, found: 402.2092

(1*S*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylhex-5-en-1-amine (25)



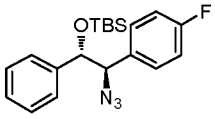
Prepared as described above starting from cyanohydrin **14** (200 mg, 0.89 mmol) and phenylmagnesium bromide (0.89 mL of a 3.0 M solution in Et_2O, 2.67 mmol, 3.0 equiv). Column chromatography (EtOAc/heptane, 1:7→1:1) yielded **25** (142 mg, 52%) as a yellowish oil. R_f 0.43 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −3.9 (*c* 1.60, CH_2Cl_2). IR (ATR): 2952, 2928, 2885, 2855, 1254, 1081, 835, 774, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.27 (m, 5H), 5.71 (ddt, *J* = 10.2, 16.9, 6.5 Hz, 1H), 4.95-4.86 (m, 2H), 4.04 (d, *J* = 4.3 Hz, 1H), 3.85 (ddd, *J* = 4.3, 4.3, 7.6 Hz, 1H), 1.66-1.55 (m, 2H), 1.34-1.24 (m, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.7, 138.6, 128.1, 127.3, 126.9, 114.3, 76.3, 59.8, 30.3, 29.7, 25.9, 18.1, −4.5, −4.6. HRMS (ESI) *m/z* calcd for $C_{18}H_{32}NOSi$ $(M+H)^+$: 306.2253, found: 306.2235.

(1*S*,2*R*)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-1,2-diphenylethane (26)



To a solution of NaN_3 (261 mg, 4.01 mmol, 6.0 equiv) in a mixture of H_2O/CH_2Cl_2 (4 mL, 1:1 v/v) at 0 °C, was added Tf_2O (337 µL, 2.01 mmol, 3.0 equiv). The reaction mixture was stirred at 0 °C for 2h. After quenching with saturated aqueous $NaHCO_3$, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 3 mL). The organic layers were combined to afford 5 mL of TfN_3 solution. This TfN_3 was then added to a solution of amino alcohol **16** (219 mg, 0.67 mmol) in MeOH (15 mL), followed by H_2O (5 mL), a solution of $CuSO_4$ (11 mg, 10 mol %) in MeOH (0.5 mL), and Et_3N (297 µL, 2.01 mmol, 3.0 equiv). The reaction mixture was stirred overnight at rt. Then saturated aqueous $NaHCO_3$ (25 mL) was added and the organic solvents were evaporated. The aqueous residue was extracted with EtOAc (3 × 25 mL) and the organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (EtOAc/heptane, 1:7→1:3) afforded **26** (235 mg, 99%). R_f 0.71 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −0.8 (*c* 0.96, CH_2Cl_2). IR (ATR): 2950, 2928, 2855, 2103, 1255, 1099, 838, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.21 (m, 10H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 0.74 (s, 9H), −0.22 (s, 3H), −0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.9, 137.0, 128.2, 128.1, 127.9, 127.3, 78.7, 72.2, 25.6, 18.0, −5.0, −5.6.

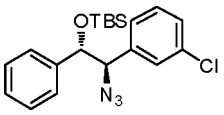
(1*S*,2*R*)-2-Azido-1-(*tert*-butyldimethylsilyloxy)- 2-(4-fluorophenyl)-1-phenylethane (27)



Prepared as described above starting from amino alcohol **17** (194 mg, 0.56 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **27** (194 mg, 93%) as a colorless oil. R_f 0.74 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +3.6 (*c* 1.63,

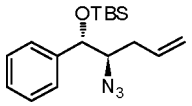
CH_2Cl_2). IR (ATR): 2954, 2929, 2856, 2104, 1510, 837, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.14 (m, 7H), 7.03-6.96 (m, 2H), 4.70 (d, J = 6.3 Hz, 1H), 4.56 (d, J = 6.3 Hz, 1H), 0.76 (s, 9H), −0.17 (s, 3H), −0.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.5 (d, J = 246.6 Hz), 140.7, 132.7 (d, J = 2.9 Hz), 129.9 (d, J = 8.1 Hz), 127.9, 127.2, 115.0 (d, J = 21.5 Hz), 78.5, 71.4, 25.6, 18.0, −4.9, −5.5.

(1*S*,2*R*)-2-Azido-1-(*tert*-butyldimethylsilyloxy)- 2-(3-chlorophenyl)-1-phenylethane (28)



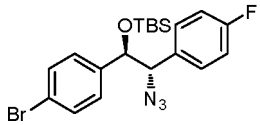
Prepared as described above starting from amino alcohol **18** (87 mg, 0.24 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **28** (89 mg, 99%) as a yellowish oil. R_f 0.70 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −0.6 (*c* 1.28, CH_2Cl_2). IR (ATR): 2952, 2923, 2889, 2851, 2103, 1469, 1258, 1093, 840 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.20 (m, 8H), 7.12-7.07 (m, 1H), 4.67 (d, J = 6.6 Hz, 1H), 4.53 (d, J = 6.6 Hz, 1H), 0.76 (s, 9H), −0.20 (s, 3H), −0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.8, 139.3, 134.2, 129.3, 128.5, 128.2, 128.1, 128.0, 127.2, 126.3, 78.5, 71.5, 25.6, 18.0, −5.0, −5.6.

(1*S*,2*R*)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-1-phenylpent-4-ene (29)



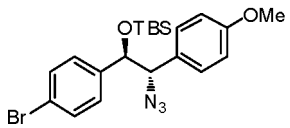
Prepared as described above starting from amino alcohol **19** (63 mg, 0.22 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **29** (62 mg, 91%) as a yellowish oil. R_f 0.73 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +100.1 (*c* 1.03, CH_2Cl_2). IR (ATR): 2954, 2929, 2894, 2858, 2110, 1257, 1094, 856, 837, 777, 701, 603 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.25 (m, 5H), 5.79 (dddd, J = 6.5, 7.2, 10.2, 17.1 Hz, 1H), 5.18-5.06 (m, 2H), 4.71 (d, J = 4.8 Hz, 1H), 3.45 (ddd, J = 4.0, 4.8, 9.6 Hz, 1H), 2.35-2,26 (m, 1H), 2.24-2.14 (m, 1H), 0.91 (s, 9H), 0.08 (s, 3H), −0.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.9, 134.4, 128.1, 127.8, 126.9, 117.7, 77.3, 67.8, 33.5, 25.8, 18.1, −4.7, −5.2.

(1*R*,2*S*)-2-Azido-1-(4-bromophenyl)-1-(*tert*-butyldimethylsilyloxy)-2-(4-fluorophenyl)ethane (30)



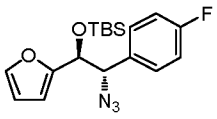
Prepared as described above starting from amino alcohol **20** (84 mg, 0.20 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **30** (78 mg, 87%) as a yellowish oil. R_f 0.68 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −18.4 (*c* 1.03, CH_2Cl_2). IR (ATR): 2954, 2928, 2855, 2105, 1509, 838, 779 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.38 (m, 2H), 7.18-7.12 (m, 2H), 7.07-6.97 (m, 4H), 4.67 (d, J = 6.1 Hz, 1H), 4.53 (d, J = 6.1 Hz, 1H), 0.78 (s, 9H), −0.16 (s, 3H), −0.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6 (d, J = 246.9 Hz), 139.6, 132.2 (d, J = 2.8 Hz), 131.1, 129.8 (d, J = 8.1 Hz), 128.8, 121.9, 115.1 (d, J = 21.5 Hz), 78.0, 71.2, 25.6, 18.0, −4.9, −5.5.

(1*R*,2*S*)-2-Azido-1-(4-bromophenyl)-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)ethane (31)



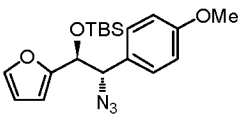
Prepared as described above starting from amino alcohol **21** (77 mg, 0.18 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **31** (64 mg, 76%) as a yellowish oil. R_f 0.73 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −2.7 (*c* 0.88, CH_2Cl_2). IR (ATR): 2954, 2927, 2855, 2104, 1513, 1251, 839, 779 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.37 (m, 2H), 7.12-7.02 (m, 4H), 6.86-6.81 (m, 2H), 4.68 (d, J = 5.9 Hz, 1H), 4.51 (d, J = 5.9 Hz, 1H), 3.81(s, 3H), 0.78 (s, 9H), −0.15 (s, 3H), −0.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.5, 139.9, 130.9, 129.3, 128.9, 128.4, 121.7, 113.6, 78.1, 71.4, 55.3, 25.6, 18.0, −4.9, −5.4.

(1*S*,2S)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(furan-2-yl)ethane (32)



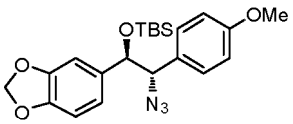
Prepared as described above starting from amino alcohol **22** (138 mg, 0.41 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **32** (98 mg, 66%) as a yellowish oil. R_f 0.73 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −0.8 (*c* 0.96, CH_2Cl_2). IR (ATR): 2958, 2928, 2855, 2105, 1510, 838, 779 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.29-7.24 (m, 2H), 7.06-7.00 (m, 2H), 6.35 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.25 (dd, *J* = 3.3, 0.8 Hz, 1H), 4.77 (d, *J* = 7.4 Hz, 1H), 4.70 (d, *J* = 7.4 Hz, 1H), 0.70 (s, 9H), −0.20 (s, 3H), −0.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6 (d, *J* = 246.8 Hz), 153.4, 142.1, 132.9 (d, *J* = 3.0 Hz), 129.7 (d, *J* = 8.2 Hz), 115.1 (d, *J* = 21.5 Hz), 110.4, 108.6, 72.0, 68.9, 25.4, 17.9, −5.4, −5.7.

(1*S*,2*S*)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)-1-(furan-2-yl)ethane (33)



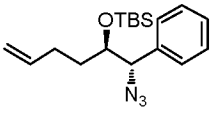
Prepared as described above starting from amino alcohol **23** (155 mg, 0.45 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **33** (107 mg, 64%) as a yellowish oil. R_f 0.70 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +18.8 (*c* 0.90, CH_2Cl_2). IR (ATR): 954, 2924, 2850, 2104, 1514, 1250, 838, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.24-7.19 (m, 2H), 6.89-6.84 (m, 2H), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.25 (dd, *J* = 3.2, 0.7 Hz, 1H), 4.73 (d, *J* = 7.4 Hz, 1H), 4.70 (d, *J* = 7.4Hz, 1H), 3.81 (s, 3H), 0.71 (s, 9H), −0.19 (s, 3H), −0.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.5, 153.8, 141.9, 129.1, 128.3, 113.7, 110.3, 108.4, 72.0, 69.2, 55.3, 25.5, 17.9, −5.4, −5.6.

(1*R*,2*S*)-2-Azido-1-(3,4-methylenedioxylphenyl)-1-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)ethane (34)



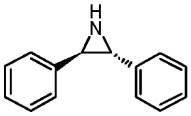
Prepared as described above starting from amino alcohol **24** (175 mg, 0.44 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **34** (167 mg, 90%) as a yellowish oil. R_f 0.77 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +10.9 (*c* 1.30, CH_2Cl_2). IR (ATR): 2950, 2924, 2885, 2850, 2101, 1245, 835 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.17-7.12 (m, 2H), 6.88-6.83 (m, 2H), 6.76 (d, *J* = 1.6 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.63 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.96 (d, *J* = 1.5 Hz, 1H), 5.95 (d, *J* = 1.5 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.47 (d, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 0.76 (s, 9H), −0.18 (s, 3H), −0.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.6, 147.5, 147.2, 135.3, 129.5, 129.2, 120.9, 113.7, 107.7, 107.6, 101.1, 78.5, 71.9, 55.4, 25.8, 18.1, −4.8, −5.3.

(1*S*,2*R*)-1-Azido-2-(*tert*-butyldimethylsilyloxy)-1-phenylhex-5-ene (35)



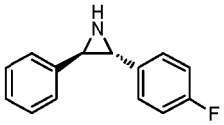
Prepared as described above starting from amino alcohol **25** (142 mg, 0.46 mmol). Column chromatography (EtOAc/heptane, 1:7→1:3) yielded **35** (115 mg, 76%) as a yellowish oil. R_f 0.77 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +44.3 (*c* 1.79, CH_2Cl_2). IR (ATR): 2950, 2928, 2885, 2855, 2100, 1253, 835, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.26 (m, 5H), 5.75 (ddt, *J* = 10,2, 16.9, 6.6 Hz, 1H), 5.01-4.90 (m, 2H), 4.56 (d, *J* = 5.1 Hz, 1H), 3.91 (ddd, *J* = 6.6, 5.0, 4.3 Hz, 1H), 2.23-2.10 (m, 1H), 2.10-1.97 (m, 1H), 1.75-1.65 (m,1H), 1.53-1.43 (m, 1H), 0.89 (s, 9H), 0.05 (s, 3H), −0.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 137.1, 128.4, 128.0, 127.8, 114.6, 75.4, 69.7, 31.5, 29.0, 25.8, 18.0, −4.6, −4.7.

(2*R*,3*R*)-2,3-Diphenylaziridine (37)



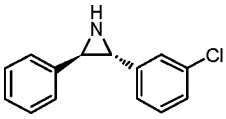
To a solution of azide **26** (142 mg, 0.41 mmol) in THF (4 mL) at 0 °C was added TBAF (480 μL of a 1.0 M solution in THF, 0.48 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 1 h. After quenching with saturated aqueous NH_4Cl (4 mL) the product was extracted with EtOAc (3 × 8 mL). The resulting organic layers were combined, washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Then, the crude product was redissolved in MeCN (4 mL) and PPh_3 (129 mg, 0.48 mmol, 1.2 equiv) was added. After refluxing the reaction mixture for 2 h, the solution was allowed to cool to rt. The solvent was then evaporated and the product was purified by column chromatography (EtOAc/heptane, 1:7→1:2) to give pure **37** (36 mg, 60%) as a colorless oil. R_f 0.56 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +331 (*c* 1.27, CH_2Cl_2) {ref.[8] $[\alpha]_D^{20}$ +328.8 (*c* 1.25, $CHCl_3$)}. IR (ATR): 3287, 3058, 3023, 1498, 1191 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.5-7.2 (m, 10H), 3.3-2.8 (br s, 2H), 1.6-1.2 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.5, 128.6, 127.3, 125.5, 43.7. HRMS (ESI) *m/z* calcd for $C_{14}H_{14}N$ $(M+H)^+$: 196.1126, found: 196.1115. Data are in agreement with literature.[45]

(2*R*,3*R*)-2-(4-Fluorophenyl)-3-phenylaziridine (38)



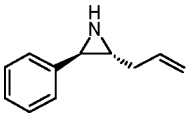
Prepared as described above starting from azide **27** (301 mg, 0.81 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **38** (82 mg, 47%) as a yellowish oil. R_f 0.41 (EtOAc/toluene, 1:4). $[\alpha]_D^{20}$ +232 (*c* 1.35, CH_2Cl_2). IR (ATR): 3028, 1511, 1230, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.23 (m, 7H), 7.07-7.00 (m, 2H), 3.12 (d, *J* = 2.0 Hz, 1H), 3.03 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.7 (d, *J* = 245.4 Hz), 139.3, 134.8 (d, *J* = 3.1 Hz), 128.7, 127.4, 126.7 (d, *J* = 8.0 Hz), 125.4, 115.0 (d, *J* = 21.6 Hz), 43.8, 42.8. HRMS (ESI) *m/z* calcd for $C_{14}H_{13}FN$ $(M+H)^+$: 214.1032, found: 214.1037.

(2*R*,3*R*)-2-(3-Chlorophenyl)-3-phenylaziridine (39)



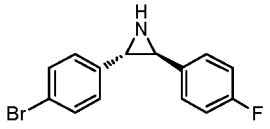
Prepared as described above starting from azide **28** (64 mg, 0.16 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **39** (27 mg, 89%) as a yellowish oil. R_f 0.54 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +204 (*c* 0.47, CH_2Cl_2). IR (ATR): 3068, 3022, 2922, 1598, 776, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.15 (m, 9H), 3.11 (s, 1H), 3.05 (s, 1H), 1.81 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.8, 139.1, 134.6, 129.8, 128.7, 127.5, 127.4, 125.7, 125.4, 123.9, 44.1, 42.7. HRMS (ESI) *m/z* calcd for $C_{14}H_{13}ClN$ $(M+H)^+$: 230.0737, found: 230.0738.

(2*R*,3*R*)-2-Allyl-3-phenylaziridine (40)



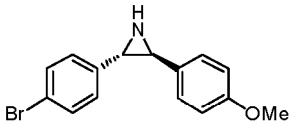
Prepared as described above starting from azide **29** (85 mg, 0.27 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **40** (22 mg, 51%) as a yellowish oil. R_f 0.48 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +36 (*c* 0.55, CH_2Cl_2). IR (ATR): 2924, 2850, 915, 747, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.17 (m, 5H), 5.89 (dddd, *J* = 6.5, 6.5, 10.2, 16.9 Hz, 1H), 5.20-5.13 (m, 1H), 5.13-5.08 (m, 1H), 2.73 (d, *J* = 2.7 Hz, 1H), 2.43-2.29 (m, 2H), 2.19 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.2, 134.2, 128.5, 127.0, 125.6, 117.1, 40.5, 38.6, 37.8. HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N$ $(M+H)^+$: 160.1126, found: 160.1135.

(2*S*,3*S*)-2-(4-Bromophenyl)-3-(4-fluorophenyl)aziridine (41)



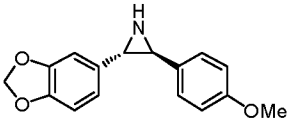
Prepared as described above starting from azide **30** (50 mg, 0.11 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **41** (24 mg, 73%) as a yellowish oil. R_f 0.64 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −216 (*c* 1.18, CH_2Cl_2). IR (ATR): 3300, 2920, 2846, 1510, 1488, 1228, 805 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.44 (m, 2H), 7.26-7.10 (m, 4H), 7.09-7.00 (m, 2H), 3.02 (br s, 2H), 1.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.2 (d, *J* = 245.9 Hz), 138.4, 134.9, 131.7, 127.2, 127.0 (d, *J* = 8.3 Hz), 121.1, 115.6 (d, *J* = 21.6 Hz), 43.1. HRMS (ESI) *m/z* calcd for $C_{14}H_{12}BrFN$ $(M+H)^+$: 292.0137, found: 292.0127.

(2*S*,3*S*)-2-(4-Bromophenyl)-3-(4-methoxyphenyl)aziridine (42)



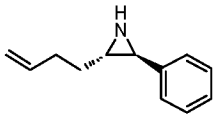
Prepared as described above starting from azide **31** (58 mg, 0.12 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **42** (19 mg, 53%) as a yellowish oil. R_f 0.59 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −171 (*c* 0.38, CH_2Cl_2). IR (ATR): 2954, 2922, 2853, 1514, 1249, 802 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.44 (m, 2H), 7.21-7.14 (m, 4H), 6.92-6.87 (m, 2H), 3.81 (s, 3H), 3.05 (br s, 1H), 2.97 (br s, 1H), 1.51 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 138.8, 131.6, 131.2, 127.2, 126.5, 120.1, 114.2, 55.3, 43.7, 42.5. HRMS (ESI) *m/z* calcd for $C_{15}H_{15}BrNO$ $(M+H)^+$: 304.0337, found: 304.0340.

(2*S*,3*S*)-2-(3,4-Methylenedioxylphenyl)-3-(4-methoxyphenyl)aziridine (45)



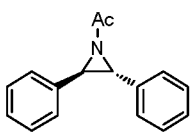
Prepared as described above starting from azide **34** (140 mg, 0.33 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **45** (47 mg, 54%) as a yellowish oil. R_f 0.48 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −133 (*c* 0.81, CH_2Cl_2). IR (ATR): 3006, 2958, 2898, 1513, 1247, 1306, 800 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21-7.16 (m, 2H), 6.92-6.86 (m, 2H), 6.79-6.74 (m, 3H), 5.95 (s, 2H), 3.81 (s, 3H), 3.01 (s, 1H), 2.97 (s, 1H), 1.46 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 148.0, 146.8, 133.8, 131.6, 126.5, 119.1, 114.1, 108.3, 105.7, 101.0, 55.3, 43.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{16}NO_3$ $(M+H)^+$: 270.1130, found: 270.1134.

(2*S*,3*S*)-2-(But-3-enyl)-3-phenylaziridine (46)



Prepared as described above starting from azide **35** (115 mg, 0.35 mmol). Column chromatography (EtOAc/heptane, 1:7→1:2) yielded **46** (27 mg, 46%) as a yellowish oil. R_f 0.40 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −51.8 (*c* 1.15, CH_2Cl_2). IR (ATR): 3067, 2980, 2920, 2842, 742, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.15 (m, 5H), 5.87 (ddt, *J* = 10.2, 16.9, 6.7 Hz, 1H), 5.10-5.03 (m, 1H), 5.02-4.97 (m, 1H), 2.71 (d, *J* = 1.9 Hz, 1H), 2.37-2.00 (m, 3H), 1.73-1.60 (m, 2H), 0.69 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.3, 137.8, 128.4, 126.9, 125.5, 115.1, 41.3, 36.9, 31.7, 31.5. HRMS (ESI) *m/z* calcd for $C_{12}H_{16}N$ $(M+H)^+$: 174.1283, found: 174.1289.

(2*R*,3*R*)-1-Acetyl-1,2-diphenylaziridine (47)



To a solution of aziridine **37** (20 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) were added, pyridine (24.8 µL, 0.30 mmol, 3.0 equiv) and acetic anhydride (29.0 µL, 0.30 mmol, 3.0 equiv). The reaction mixture was stirred for 1½ h at rt, after which the mixture was quenched with H_2O (2 mL). The product was then extracted with CH_2Cl_2 (3 × 2 mL) and the resulting organic layers were combined, dried and concentrated *in vacuo*.

Column chromatography (EtOAc/heptane, 1:7→1:2) afforded pure **47** (7 mg, 29%). R_f 0.57 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +160 (*c* 0.20, CH_2Cl_2). e.e 96% (HPLC eluent hexane: ethanol = 80:20, flow 1.0 mL/min); $R_{t,1}$ = 7.69 min (*trans*), $R_{t,2}$ = 8.32 min (*cis*). IR (ATR): 1629, 1365, 1208, 698, 618, 610 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.25 (m, 10H), 3.77 (s, 2H), 1.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.8, 135.7, 128.8, 128.0, 126.3, 48.1, 24.8. HRMS (ESI) *m/z* calcd for $C_{16}H_{16}NO$ $(M+H)^+$: 238.1232, found: 238.1230.

2.9 References and notes

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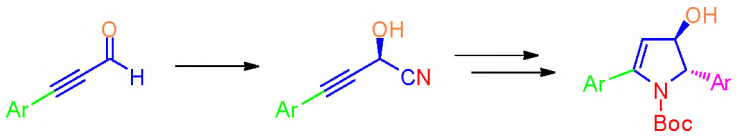
Chapter 3

Enantioselective Chemoenzymatic Synthesis of 4-Hydroxy-2-pyrrolines



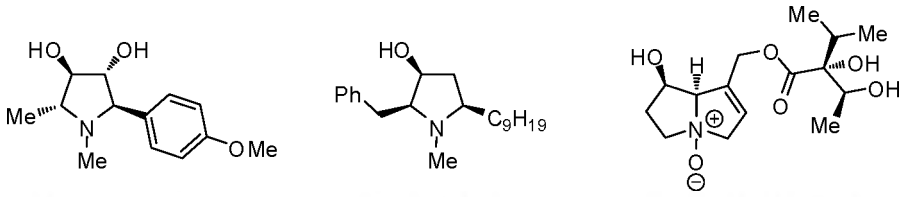
A novel route toward functionalized pyrrolines starting from propargylic aldehydes was developed. Key steps involve hydroxynitrile lyase-catalyzed asymmetric hydrocyanation of propargylic aldehydes and gold-catalyzed cyclization of substituted acetylene-containing amino alcohols. The resulting 2,5-disubstituted-4-hydroxy-2-pyrrolines are potentially useful scaffolds and could be used for the synthesis of functionalized pyrrolidines and biologically active natural products.

Part of this chapter will be published in: Ritzen, B.; Richelle, G. J. J.; Brocken, L.; van Delft, F. L.; Rutjes, F. P. J. T. Enantioselective Chemoenzymatic Synthesis of 4-Hydroxy-2-pyrrolines, *manuscript in preparation*.

3.1 Introduction

Functionalized pyrrolidines and pyrrolines are important classes of nitrogen heterocyclic compounds and constitute common motifs displayed in a wide array of biologically active compounds, including natural products and pharmaceutically relevant molecules.[1,2] Members of these compound classes show therapeutic potential such as anti-depressant,[3] anti-histaminic,[4] anti-inflammatory,[5] anti-tumor,[6] analgesic[7] and anti-parkinson activity.[8] A few examples include codonopsinine (**1**) which has been shown to possess hypotensive activity,[9] preussin (**2**) which is known to induce apoptosis in human tumor cells,[10] and indicine *N*-oxide (NSC 132319, **3**), an alkaloid isolated from *Heliotropium indicum*, which was used in clinical trials as an antineoplastic agent (Figure 3.1).[11]

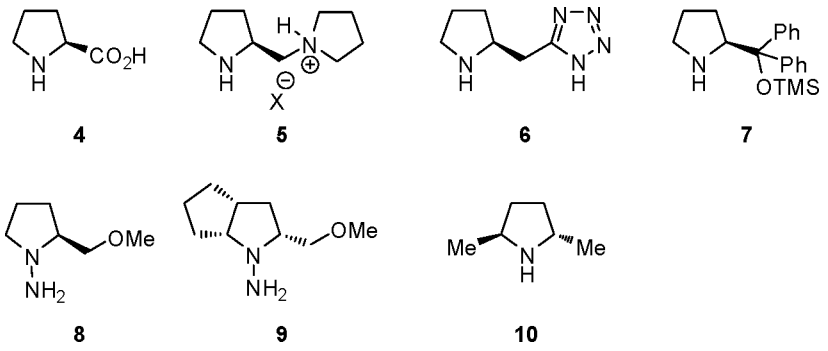
Figure 3.1 *Biologically active pyrrolidines and pyrrolines.*



1 codonopsinine **2** preussin **3** indicine *N*-oxide

Apart from the pharmaceutical applications, these moieties have also witnessed widespread use as organocatalysts and chiral auxiliaries or ligands for asymmetric synthesis. Since the pioneering studies in the early 1970s, the field of organocatalysis has grown spectacularly. By now, many more pyrroli(di)ne-based reagents[12] and catalysts[13,14] have been designed some of which are depicted in Figure 3.2.

Figure 3.2. *Representative pyrrolidine-based structures in asymmetric synthesis.*



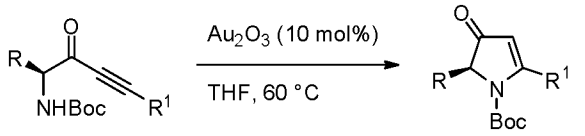
4 **5** **6** **7**

8 **9** **10**

Over the last two decades, a plethora of synthetic methods for the synthesis of functionalized nitrogen heterocycles have been developed[15] and the search for new synthetic methodologies is still ongoing.[16] Recently, increasing attention has been drawn to the use of gold-catalysis for the synthesis of nitrogen heterocyclic ring systems.[17] The ability of gold to act as a soft Lewis acid toward unsaturated carbon-carbon bonds has opened new doors for organic chemists to synthesize complex carbo- and heterocyclic structures in an efficient and mild way.

A recent example is provided by the group of Uriac, who reported a convenient route for synthesizing substituted pyrrolin-4-ones *via* gold catalysis.[18] By using a catalytic amount of Au_2O_3, they were able to isolate **12** in nearly quantitative yield without any epimerization (Scheme 3.1).

Scheme 3.1 *Gold-catalyzed synthesis of pyrrolin-4-ones.*



11

R = Me, *i*Pr, Bn, *sec*-Bu

R^1 = *n*Pr, Ph

12, 85-95% yield

up to 99% ee

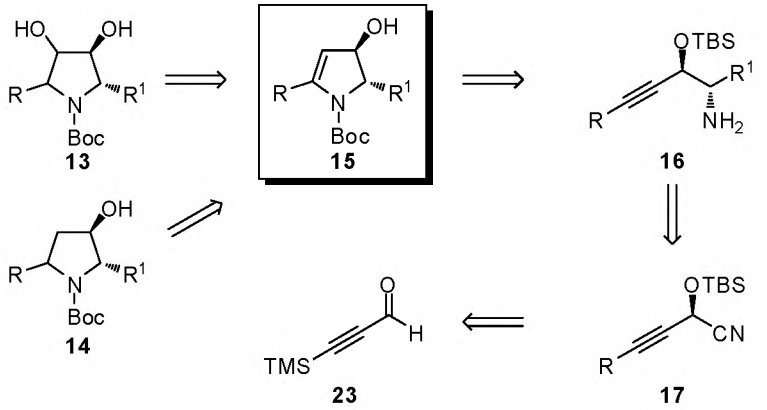
Inspired by the opportunities of gold-catalysis and the general relevance of pyrrol(id)ines, we set out to develop new and flexible strategies that would allow for stereoselective construction of highly functionalized pyrrol(id)ine-based building blocks. In addition, such a new approach may also be used to prepare series of pyrrol(id)ine derivatives, which could be

relevant in medicinal chemistry applications. Recently, we reported a novel strategy for the synthesis of functionalized aziridines[19] and morpholines[20] starting from enantiopure cyanohydrins obtained from the corresponding aldehydes *via* hydroxynitrile lyase (HNL)-mediated asymmetric hydrogen cyanide addition. We anticipated that the latter chemoenzymatic reaction in combination with gold-catalysis should also provide a basis for efficient entries into a variety of functionalized hydroxylated pyrrol(id)ines **13**–**15**.

3.2 Retrosynthetic strategy

Retrosynthetic analysis of the target 4-hydroxy-2-pyrrolines **15**, which can be considered as key precursor for synthesis of various pyrrolidines **13** and **14**, might be synthesized *via* a gold-catalyzed 5-*endo*-dig cyclization of the acetylenic amino alcohol **16** (Scheme 3.2). Installation of the homopropargylic stereogenic center may occur by performing a Grignard addition on cyanohydrin **17** followed by stereocontrolled imine reduction. The cyanohydrin **17**, in turn, could arise from HNL-mediated addition of hydrogen cyanide onto 3-(trimethylsilyl)-2-propynal (**23**), followed by substrate diversification at the terminal position of the alkyne. We reasoned that such a transformation would hold considerable potential since facile removal of the TMS group would offer the possibility to introduce a range of aromatic and aliphatic groups *via* Pd-catalyzed cross-coupling.

Scheme 3.2 *Retrosynthetic strategy to enantiopure 4-hydroxy-2-pyrrolines.*



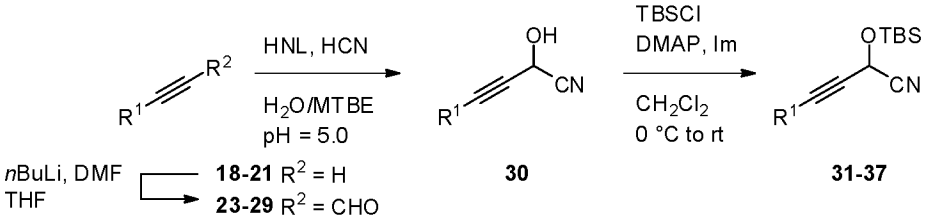
3.3 Chemoenzymatic asymmetric cyanohydrin formation

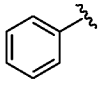
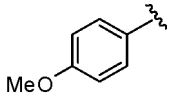
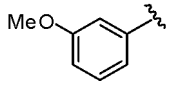
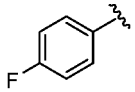
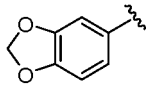
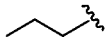
In the first generation synthesis, we commenced by making key intermediate **31** from the commercially available TMS-protected acetylenic aldehyde **23** *via* HNL-mediated asymmetric hydrogen cyanide addition. We were pleased to find that 3-(trimethylsilyl)-2-propynal (**23**) was well accepted by (*S*)-HNL providing the desired product **31**, after TBS-protection of the hydroxyl group, in good yield (83%) and excellent ee of 99% (Table 3.1, entry 1). The intrinsic instability of unprotected cyanohydrins required immediate *O*-protection (TBSCl, DMAP, imidazole) in order to prevent racemization. For the next step in the synthesis, being removal of the trimethylsilyl group, we chose to use slightly basic conditions (K_2CO_3, MeOH) in order to prevent deprotection of the hydroxyl group. Unfortunately, after having screened several conditions, all deprotection attempts failed and led merely to decomposition of the starting compound. Subjection to various fluoride sources (TBAF, HF, H_2SiF_6) under different conditions again only showed decomposition of the starting material. Replacement of the TBS-group by a THP-protecting group did not improve the results either.

In response to these results, the initial strategy to the target molecules **15** was redesigned. Instead of starting from the TMS-protected aldehyde **23**, which would be diversified after the enzymatic step, we now chose to use functionalized propargylic aldehydes that were then subjected to the HNL-catalyzed hydrocyanation. It is interesting to note that among the numerous examples of HNL-catalyzed hydrocyanations of aldehydes, additions onto α,β-acetylenic aldehydes are significantly less abundant.[21] During examination of the substrate scope, it appeared that a rather limited number of α,β-acetylenic aldehydes were commercially available. In fact, 3-phenyl-2-propynal (**24**) was the only substrate that could directly be purchased from chemical suppliers. From a practical point of view, fast and facile access to these building blocks is a prerequisite. Therefore, our first synthetic subgoal was the development of an efficient route toward these compounds. Previously, Journet *et al.* reported a highly efficient approach for the synthesis of α,β-acetylenic aldehydes from terminal alkynes using DMF as the formylating reagent.[22] We were pleased to find that using this methodology, substrates **25–27** could be readily obtained in acceptable yields of 61–73% (entries 3–5). Since terminal alkyne aldehyde **28** is also not commercially available, access was accomplished by performing a two-step Corey–Fuchs[23] reaction sequence on piperonal furnishing in the first step the dibromoalkene by reaction with tetrabromomethane and

triphenylphosphine. Next, dehydrohalogenation under basic conditions with lithium base (LDA) generates a bromoalkyne intermediate which undergoes a metal-halogen exchange providing terminal alkyne **21** in 53% yield over two steps. Subsequent subjection to the above mentioned formylating conditions led to aldehyde **28** in a satisfactory yield of 68% (entry 6). In case of aldehyde **29**, a different strategy was undertaken. In our hands, rapid access to this compound was achieved by PCC-oxidation of commercially available 2-hexynol (**22**) furnishing the desired precursor in an acceptable yield of 42% (entry 7).

Table 3.1 *HNL-mediated cyanohydrin formation and protection.*



entry	s.m.	R^1	product	yield (%)[a]	enzyme	product	yield (%)[a]	ee (%)[b]	config.
1	–	TMS	**23**[c]	–	(*S*)-HNL	**31**	83	>99	(*S*)
2	–		**24**[c]	–	(*R*)-HNL	**32**	86	>95	(*R*)
3	**18**		**25**	71	(*S*)-HNL	**33**	81	>99	(*S*)
4	**19**		**26**	61	(*S*)-HNL	**34**	80	>99	(*S*)
5	**20**		**27**	73	(*S*)-HNL	**35**	22	93	(*S*)
6	**21**[d]		**28**	68	(*S*)-HNL	**36**	92	>99	(*S*)
7	**22**[e]		**29**	42	(*S*)-HNL	**37**	–	–	–

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC analysis. [c] Commercially available. [d] Obtained *via* Corey-Fuchs reaction on piperonal. [e] Obtained *via* PCC-oxidation of 2-hexynol (**22**).

As can be seen from Table 3.1, the enantiomeric purity and the chemical yield after the HNL reaction are for the aryl-substituted aldehydes in virtually all cases excellent. The only exception seems to be 3-(4-fluorophenyl)propiolaldehyde (**27**), which is obviously not a good

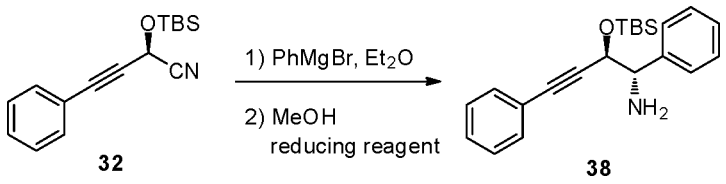
substrate for the enzyme (entry 5). In parallel to the enzyme catalyzed-reaction, the non-enzymatic cyanohydrin formation also took place although at a lower rate at this pH value. However, with difficult substrates, like the fluorinated aldehyde **27**, the spontaneous addition reaction of HCN, competed in such a way that the enantiopurity of the product (**35**) was reduced. To obtain a most optimal result for substrate **27**, the reaction was stopped at a preliminary stage before reaching full conversion, resulting in a lower isolated yield of 22%, but a rather good ee of 93%.

In a publication by Griengl *et al.*,[21] the aliphatic aldehyde **29** was obtained in 62% isolated yield and 98% enantioselectivity. Remarkable is that in contrast to their findings, in our hands no transformation of aldehyde **29** into the desired product **37** was observed. For the latter two substrates **27** and **29**, addition of larger amounts of the enzyme also did not seem to improve the yield or enantiopurity.

3.4 Synthesis of the acetylenic amino alcohols

With the availability of a suitable procedure for the synthesis of the acetylenic cyanohydrins **32**–**37**, the stage was set for performing the Grignard addition. Much to our satisfaction, when submitted to Grignard reagents, TLC and mass analyses of the crude reaction mixture revealed that cyanohydrin **32** underwent a successful transformation into the corresponding imine.

Table 3.2 *Grignard addition and reducing agent screening.*



32 **38**

entry	reducing reagent	T (°C)	yield (%)[a]	*syn*/*anti*[b]	de (%)[b]
1	$NaBH_4$	–20	44	1:3	50
2	$NaBH_4$	–78	46	1:3.5	52
3	$LiBH_4$	–78	42	1:2.5	43
4	L-selectride	–78	–	–	
5	$LiEt_3BH$	–78	–	–	
6	$NaBH_3CN$	–78	–	–	
7	$Zn(BH_4)_2$	–78	57	1:8	78

[a] Isolated yield after two steps after column chromatography. [b] Determined by ^{1}H-NMR of the crude reaction mixture.

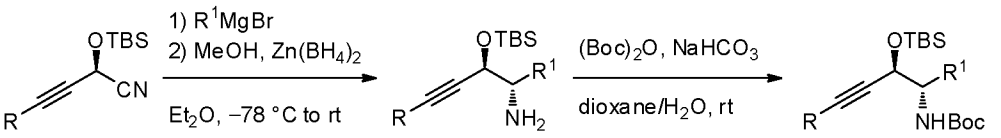
Stereoselective imine reduction to the corresponding acetylenic amino alcohols was first investigated using sodium borohydride. As already pointed out in Section 2.4, sodium borohydride reduction at 0 °C has been proven to be very effective for this type of reduction furnishing almost exclusively the *anti*-stereoisomer. However, our first attempt afforded amino alcohol **38** in 44% yield as a mixture of distereoisomers with a disappointing 1:3 *syn*/*anti* ratio (Table 3.2, entry 1). Analyzing this result, we reasoned that lowering the reaction temperature might be beneficial for the stereoselectivity and the yield of amino alcohol **38**. Unfortunately, lowering the temperature to –78 °C only slightly improved the *syn*/*anti* ratio to 1:3.5, while the yield remained the same (entry 2). Replacement of $NaBH_4$ by $LiBH_4$ was not a fortuitous choice, since the *syn*/*anti* ratio even decreased to 1:2.5 giving the product in comparable yield (entry 3). It was clear from these results that both hydride sources would not be the reducing agent of choice so that we turned our attention to more bulky hydride sources. However, subjection of the imine to L-selectride and $LiEt_3BH$ (entries 4 and 5) failed to give the desired product. Considering this, it was concluded that these reducing agents were too sterically hindered thereby hampering attack onto the imine. In case of $NaBH_3CN$, no conversion was observed at all indicating that this reagent might be too mild for reducing the imine at –78 °C (entry 6). Fortunately, this problem could be overcome by switching to $Zn(BH_4)_2$ at low temperature giving the amino alcohol **38** in an acceptable yield

of 57% as an inseparable mixture of diastereoisomers with a *syn/anti* ratio of 1:8 (entry 7). In comparison to $LiBH_4$ and $NaBH_4$, the usage of $Zn(BH_4)_2$ seems to considerably improve the chelation process. Indeed, literature reports on $Zn(BH_4)_2$ indicate that in case of chemoselective reduction of β-keto esters to the corresponding β-hydroxy esters, improved stereocontrol can be easily achieved due to the better coordinating ability of zinc with the carbonyl group of the ester.[24]

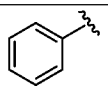
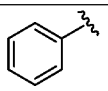
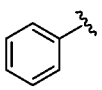
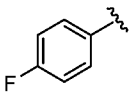
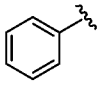
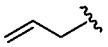
Encouraged by these results, we set out to apply this one–pot methodology in the synthesis of substituted cyanohydrins **33–36** using various Grignard reagents (Table 3.3). As expected, applying these conditions to the other cyanohydrins resulted in the formation of the *anti*–amino alcohols in satisfactory yields of 42–73% and with satisfactory *syn/anti*-ratios. The first attempts to separate the major *anti*-isomer from the minor *syn*-amino alcohol *via* column chromatography proved to be hard. To prevent tedious and lengthy chromatographic purification, we decided to separate both isomers in a later stage of the synthesis.

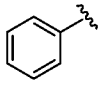
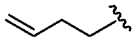
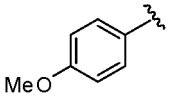
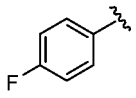
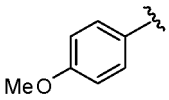
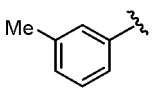
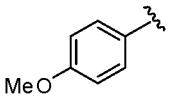
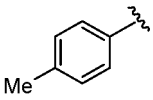
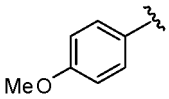
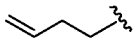
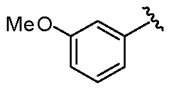
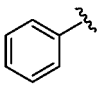
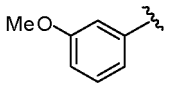
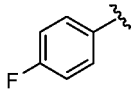
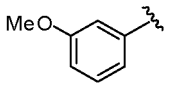
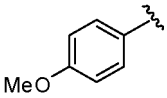
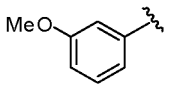
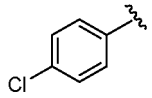
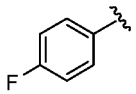
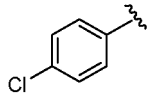
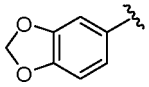
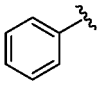
Surprisingly, no conversions into the desired products were observed in case of aliphatic Grignard reagents and aromatic Grignard reagents bearing a methoxy or methyl substituent. After closer examining these results, it occurred to us that the more-electron rich Grignard reagents refused to give the desired products. A logical explanation for these results can lie in the fact that these reagents tend to act more as a base because of the higher reactivity of the reagent, favoring competitive α-deprotonation of the cyanohydrin.

Table 3.3 *Grignard addition, reduction, and Boc-protection.*



32-36 **38-51** **52-65**

entry	s.m.	R	R^1	amino alcohol	yield (%)[a]	*syn/anti*[b]	prod	yield (%)[a]	*syn/anti*[b]	config.
1	**32**			**38**	58	1:8	**52**	73	1:17	(*R*,*S*)
2	**32**			**39**	57	1:7	**53**	72	1:10	(*R*,*S*)
3	**32**			**40**	–[c]	–	**54**	–	–	–

4	**32**			**41**	–[c]	–	**55**	–	–	–
5	**33**			**42**	42	1:30	**56**	70	1:60	(*S*,*R*)
6	**33**			**43**	–[c]	–	**57**	–	–	–
7	**33**			**44**	–[c]	–	**58**	–	–	–
8	**33**			**45**	–[c]	–	**59**	–	–	–
9	**34**			**46**	53	1:6	**60**	75	1:6	(*S*,*R*)
10	**34**			**47**	73	1:7	**61**	80	1:12	(*S*,*R*)
11	**34**			**48**	–[c]	–	**62**	–	–	–
12	**34**			**49**	66	1:6	**63**	85	1:7	(*S*,*R*)
13	**35**			**50**	56	1:5	**64**	79	1:5	(*S*,*R*)
14	**36**			**51**	69	1:7	**65**	74	1:8	(*S*,*R*)

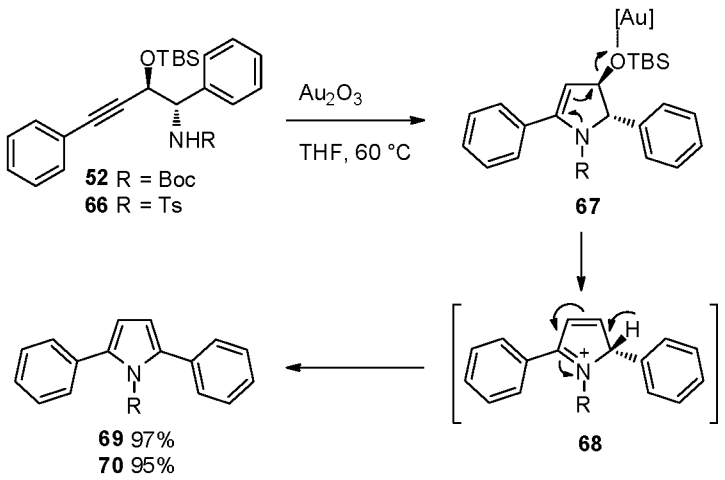
[a] Isolated yield after two steps after column chromatography. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] n.d. = not determined.

3.5 Synthesis of the pyrroline scaffold

Having the desired acetylenic amino alcohols in hand, subsequent protection of the amine functionality with an electron-withdrawing group was necessary in order to enhance the stability of the corresponding pyrroline. Without the protecting group, the formed enamine ring system, being in equilibrium with the corresponding imine, would be prone to side reactions and degradation. Thus, standard Boc-protection conditions smoothly furnished the corresponding carbamate analogues **52**–**65** in 70–85% yield. At this stage, the diasteromeric ratio for most of the substrates could be improved through chromatographic purification.

Completion of the synthetic route required, as the final step, gold-catalyzed 5-*endo*-dig cyclization. We decided to explore the strategy developed by Uriac as a basis for the construction of our 4-hydroxy-2-pyrroline systems. Unfortunately, initial experiments showed that treatment of **52** with the aforementioned catalyst led to rapid formation of the cyclic pyrrole **69** in almost quantitative yield (Scheme 3.3). In case of sulfonamide **66**, which was easily obtained from **38** in 85% yield, exposure under the exact same conditions as for the Boc-protected precursor **52** exclusively led to the formation of the corresponding Ts-protected pyrrole **70** in 95% yield.[25] The formation of **69** and **70** can be explained by complexation of the Au(III)-catalyst to the OTBS group which is now sufficiently activated to act as a good leaving group. Clearly, the nitrogen atom in the formed pyrroline **67** is sufficiently nucleophilic to donate its lone pair into the ring system, thereby expelling the protected hydroxyl group under formation of the *N*-acyl- or *N*-sulfonyliminium intermediate **68**.

Scheme 3.3 *Rationale for the formation of pyrrole **69** and **70**.*

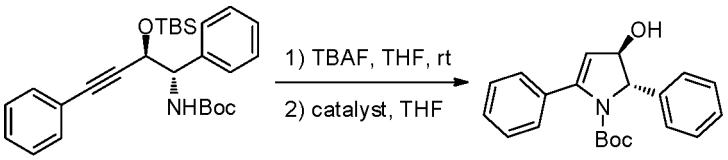


To circumvent the elimination problem, we reasoned that transformation into the free hydroxyl group of substrate **52** could offer a solution. As expected, deprotection of the TBS-protected amine **52** proceeded cleanly and afforded the product **72** in quantitative yield. Next, we turned our attention to the aforementioned cyclization conditions. Unfortunately, cyclization of the unprotected precursor was again attended with formation of large quantities of undesired pyrrole **69**. Moreover, during column chromatography we found that the pyrroline **71** was rather unstable toward silica gel since only pyrrole **69** was isolated. Luckily, treatment of silica gel with Et_3N (1% v/v) circumvented the latter problem. Repeating the same experiment, however, gave the desired product **71** in a poor yield of 37% (Table 3.4,

entry 1). Attempts at lower reaction temperature (entry 2), and using a lower amount of catalyst (entry 3) only drastically decreased the reaction rate and had a negative influence on the yield. A more successful result was obtained when the reaction was carried out at 50 °C (entry 4). Subjection of **52** to these conditions led to the rapid formation of pyrroline **71** as the sole product in a moderate 66% yield. Consequently, in identifying the optimal conditions we set out to investigate the cyclization of substrate **52** with a series of catalysts. Switching to other gold species such as AuCl, $AuCl_3$, and $AuBr_3$ proved to be less successful (entries 5–7). However, for many gold-catalyzed transformations, a most convenient catalyst proved to be the [$Au(PPh_3)Cl$] complex. Indeed, when using this catalyst a higher yield of 71% was achieved (entry 8). In our hands, however, $NaAuCl_4 \cdot 2H_2O$ turned out to be a superior catalyst giving pyrroline **71** in 92% yield (entry 9). When a catalyst, *in situ* generated from $Au(PPh_3)Cl$ and an equimolar amount of AgOTf was used,[26] a somewhat lower yield of 83% was obtained (entry 10).

In addition to gold species, silver salts were also proven to be highly effective.[2c,27] Interestingly, exposure of **52** to AgOTf under the otherwise same conditions gave rise to the formation of **71** in a moderate 55% yield (entry 11). Subjection of **52** to other catalysts in heated THF did not lead to formation of pyrroline **71**, but gave an almost quantitative recovery of the starting material or to isolation of pyrrole **69** (entries 12–15). In case of $Pd(OAc)_2$ the formation of pyrroline **71** was comparable to that when AgOTf was used (entry 16).

Table 3.4 *Catalyst screening for 5-endo-dig cyclization of* ***52****.*



52 **71**

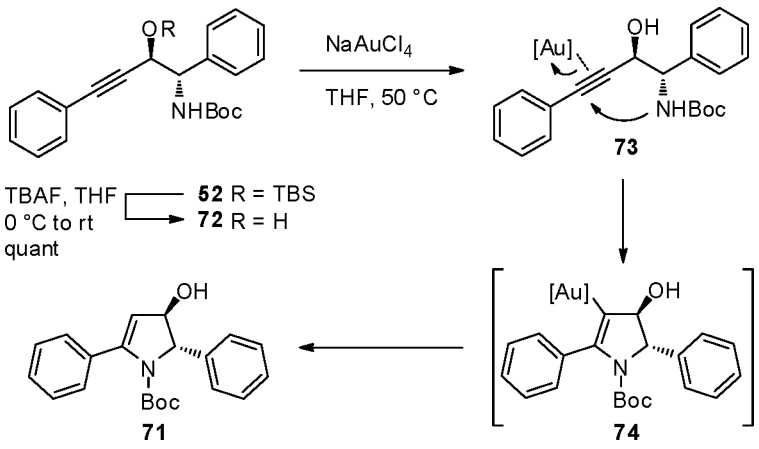
entry	catalyst[a]	temperature (°C)	yield (%)[b]
1	Au_2O_3	60	37
2	Au_2O_3	30	20[c]
3	Au_2O_3	60	31[d]
4	Au_2O_3	50	66
5	AuCl	50	49
6	$AuCl_3$	50	39

7	$AuBr_3$	50	43
8	$Au(PPh_3)Cl$	50	71
9	$NaAuCl_4 \cdot 2H_2O$	50	92
10	$AgOTf/Au(PPh_3)Cl$	50	83
11	AgOTf	50	55
12	$PtCl_2$	50	–[e]
13	$InCl_3$	50	–[f]
14	$HgCl_2$	50	–[f]
15	$Cu(OAc)_2$	50	–[f]
16	$Pd(OAc)_2$	50	53

[a] All reaction were conducted in THF using 10 mol% of the indicated catalyst. [b] Isolated yield after two steps after column chromatography. [c] Isolated yield after 17 h. [d] 5 mol % Au_2O_3. [e] Mainly pyrrole formation. [f] Only starting material was isolated.

The first step in the mechanism catalyzed by gold proceeds *via* initial coordination of the metal to the alkyne thereby polarizing the triple bond (Scheme 3.4). Nucleophilic attack from the nitrogen atom on the activated alkyne proceeds *via* π-complex **73** to give alkenyl gold complex **74** as intermediate. Finally, rapid replacement of the gold by a proton in a process called protodeauration, releases the desired pyrroline **71** and regenerates the catalytic species.

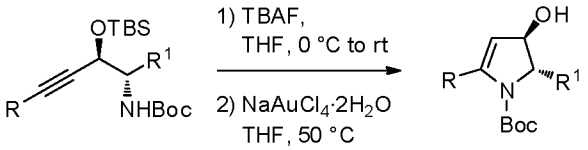
Scheme 3.4 *Gold catalyzed 5-endo-dig cyclization.*



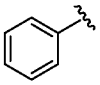
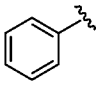
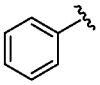
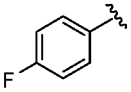
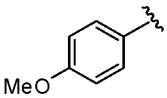
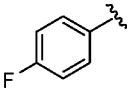
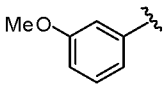
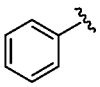
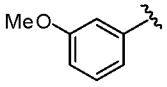
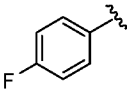
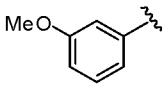
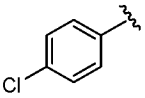
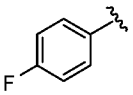
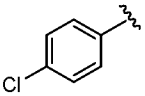
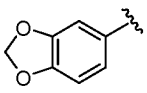
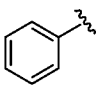
Encouraged by the facile 5-*endo*-dig cyclization of **52**, we deprotected the other compounds **53**–**65** as well prior to the gold-catalysis. Clean conversions were observed for all compounds

rendering further column chromatographic purification redundant (Table 3.5). Instead, a simple extraction was sufficient so that compounds **52–65** were directly used for the next step. To our great delight, subjection of all the precursors toward $NaAuCl_4 \cdot 2H_2O$ in THF at 50 °C furnished the desired pyrrolines **71–81** in excellent yields of 88–95% over two steps. An unexpected bonus was that at this point we were successful in fully separating both diastereoisomers *via* column chromatography.

Table 3.5 *Deprotection and gold-catalyzed cyclization.*



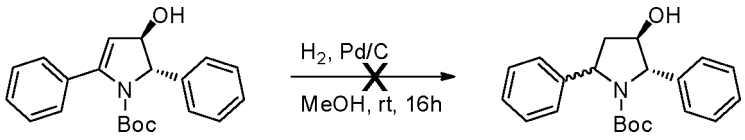
52-65 **71-81**

entry	s.m.	R	R^1	pyrroline	yield (%)[a]	config.
1	**52**			**71**	92	(*R*,*S*)
2	**53**			**75**	88	(*R*,*S*)
3	**56**			**76**	92	(*S*,*R*)
4	**60**			**77**	95	(*S*,*R*)
5	**61**			**78**	89	(*S*,*R*)
6	**63**			**79**	90	(*S*,*R*)
7	**64**			**80**	91	(*S*,*R*)
8	**65**			**81**	93	(*S*,*R*)

[a] Isolated yield after two steps after column chromatography. [b] Determined by ^{1}H-NMR of the crude reaction mixture.

To expand the synthetic opportunities of the resulting pyrrolines, we also briefly investigated functionalization of the double bond by stereoselective reduction of **71** which would be an effective manner for obtaining highly functionalized pyrrolidine derivatives. Therefore, pyrroline **71** was subjected to straightforward hydrogenation conditions using Pd on carbon under a hydrogen atmosphere (Scheme 3.5). Disappointingly, these conditions did not lead to the desired reduction of the enamide moiety, but instead gave partial decomposition of the starting material, probably as a result of hydrogenolysis at the benzylic position. At this stage only a small amount of material was left due to extensive investigations in the previous steps, and in combination with the relatively instable character of the hydroxy-pyrroline **71**, we were not able to accomplish the formation of the corresponding pyrrolidine **82**.

Scheme 3.5 *Hydrogenation of pyrrolidine* ***82****.*



71 **82**

3.6 Conclusions

In conclusion, we have developed a new and facile diastereoselective route to aryl-substituted 4-hydroxy-2-pyrrolines proceeding *via* 5-*endo*-dig Au-catalyzed cyclization of acetylene-containing amino alcohols in excellent yield. Moreover, it has been demonstrated that these compounds can be readily accessed using a one–pot Grignard addition–$Zn(BH_4)_2$ reduction sequence starting from acetylenic cyanohydrins in reasonable yield and good diastereomeric ratio. At this moment, subsequent follow-up chemistry on the formed pyrrolines to elaborate the resultant pyrrolidines appeared to be surprisingly troublesome, mostly due to the labile character of the pyrrolines. Extension of this methodology to other members of the same class of molecules is currently under investigation in our group.

3.7 Acknowledgements

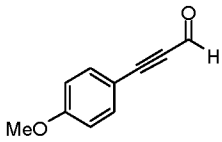
Gaston J. J. Richelle and Laurens Brocken are gratefully acknowledged for their contribution to this chapter. DSM Pharma Chemicals (Geleen, the Netherlands) is kindly acknowledged for providing the HNL enzymes.

3.8 Experimental section

General information

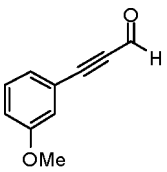
For general experimental details, see section 2.8. High Performance Liquid Chromatography (HPLC) measurements were conducted either on a HPLC apparatus equipped with a Chiralpak AD-H column (dimensions: 250 × 4.6 mm) or on a HPLC apparatus equipped with a Chiralcel OD-H column (dimensions: 250 × 4.6 mm) and peaks were detected using a UV-detector.

3-(4-Methoxyphenyl)-2-propynal (25)



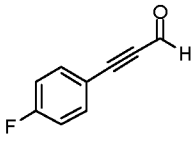
To a solution of 1-ethynyl-4-methoxybenzene **18** (2.00 g, 15.0 mmol) in dry THF (40 mL) was added dropwise *n*-butyllithium (9.38 mL of a 1.6 M solution in hexane, 1.0 equiv) at −78 °C. After 5 min, dry DMF (3.00 mL, 2.0 equiv) was added all at once at −78 °C. The reaction mixture was allowed to increase to rt and the mixture was stirred for 3h. Next, the reaction mixture was quenched with 10% aqueous KH_2PO_4 (40 mL) and Et_2O (100 mL) was added. The aqueous layer was extracted with Et_2O (3× 50 mL) and the organic layers were washed with H_2O (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified with column chromatography (CH_2Cl_2/pentane, 0:1→3:2) to afford **25** (1.66 g, 71% yield) as a yellow solid. R_f 0.38 (CH_2Cl_2/pentane, 1:4). IR (ATR) 3019, 2933, 2855, 2180, 1653, 1597, 1247, 1027, 975, 840.8, 702.5 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.40 (s, 1H), 7.58-7.55 (m, 2H), 6.93-6.90 (m, 2H) 3.86 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.8, 162.3, 135.6, 114.6, 111.3, 96.7, 88.9, 55.6. HRMS (EI) *m/z* calcd for $C_{10}H_8O_2$ 160.0524, found: 160.0525.

3-(3-Methoxyphenyl)-2-propynal (26)



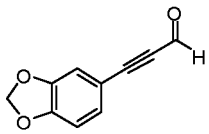
Prepared as described above starting from 1-ethynyl-3-methoxybenzene **19** (2.50 g, 19.0 mmol). Purification by column chromatography (CH_2Cl_2/pentane, 0:1→3:2) afforded **26** (1.90 g, 61% yield) as a yellow oil: R_f 0.42 (EtOAc/heptane, 1:3). IR (ATR) 3308, 2963, 2846, 2185, 1658, 1290, 1165, 1051, 1009, 715 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 7.33-7.29 (m, 1H), 7.22-7.19 (m, 1H), 7.12-7.10 (m, 1H), 7.06-7.02 (m, 1H), 3.82 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.9, 159.6, 130.0, 125.9, 120.5, 118.2, 117.8, 95.1, 88.2, 55.5. HRMS (EI) *m/z* calcd for $C_{10}H_8O_2$ 160.0524, found: 160.0522.

3-(4-Fluorophenyl)-2-propynal (27)



Prepared as described above starting from 1-ethynyl-4-fluorobenzene **20** (1.69 g, 14.1 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→2:3) afforded **27** (1.52 g, 73% yield) as a yellow solid: R_f 0.48 (EtOAc/heptane, 1:3). Mp 47.9 °C. IR (ATR) 2194, 1658, 1601, 1506, 1230, 971, 841 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.41 (s, 1H), 7.64-7.59 (m, 2H), 7.14-7.08 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.7, 164.5 (d, J = 254.7), 135.8 (d, J = 9.0 Hz), 116.5 (d, J = 22.4 Hz), 115.8, 94.1, 88.5. HRMS (EI) *m/z* calcd for C_9H_5FO 148.0324, found: 148.0326.

3-(3,4-Methylenedioxyphenyl)-2-propynal (28)

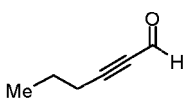


5-(2,2-Dibromovinyl)benzo[1,3]dioxole: CBr_4 (27.6 g, 2.5 equiv) was added to a solution of PPh_3 (43.7 mg, 5.0 equiv) in dry CH_2Cl_2 (500 mL) at 0 °C. After stirring for 10 min, a solution of piperonal (5.00 g, 33.3 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise with a dropping funnel. After 5 min the mixture was allowed to warm to rt and the mixture was stirred for 1 h. Next, the mixture was quenched with brine and the product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc/heptane, 0:1→3:7) afforded the dibromide (6.61 g, 65%) as a yellow solid: R_f 0.53 (EtOAc/heptane, 1:3). Mp 38.0 °C. IR (ATR) 3006, 2889, 2181, 1658, 1506, 1493, 1446, 1251, 1044, 932, 875, 836, 802, 512 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36 (s, 1H), 7.19-7.18 (m, 1H), 6.96-6.93 (m, 1H) 6.81-6.79 (m, 1H), 5.99 (s, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 147.9, 147.8, 136.4, 129.3, 123.5, 108.4, 108.3, 101.5, 88.0; HRMS (EI) *m/z* calcd for $C_9H_6Br_2O_2$ 303.8735, found: 303.8738.

5-Ethynylbenzo[1,3]dioxole: n-Butyllithium (15.3 mL of a 1.6 M solution in hexanes, 3.5 equiv) was added dropwise to a solution of diisopropylamine (3.23 mL, 3.5 equiv) in dry THF (33 mL) at –78 °C. After 5 min the reaction mixture was warmed to rt and stirred for 15 min. Then the mixture was cooled to –78 °C and added dropwise to a solution of the dibromide (2.0 g, 6.5 mmol) in dry THF (65 mL) at –78 °C. The reaction mixture was stirred for 1 h. Then the mixture was quenched with saturated aqueous NH_4Cl (50 mL) and the product was extracted with CH_2Cl_2 (3 × 80 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc/heptane, 0:1→3:7) afforded the terminal alkyne (777 mg, 81%) as a brown oil. R_f 0.65 (EtOAc/heptane, 1:4). IR (ATR) 3287, 2894, 2098, 1502, 1489, 1247, 1031, 923, 815 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.03 (dd,J = 1.6, 8.0 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 8.0, 1H) 5.98 (s, 2H), 2.97 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 148.4, 147.5, 127.0, 115.4, 112.2, 108.6, 101.5, 83.7, 75.7. HRMS (EI) *m/z* calcd for $C_9H_6O_2$ 146.0368, found: 146.0366.

Prepared as described above starting from the corresponding alkyne (756 mg, 5.18 mmol). Purification by column chromatography (EtOAc/heptane, 0:1 → 3:7) afforded aldehyde **28** (614 mg, 68% yield) as a yellow solid. R_f 0.42 (EtOAc/heptane, 1:3). Mp 68.6 °C. IR (ATR) 2906, 2176, 1653, 1485, 1446, 1256, 1213, 1031, 890 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.38 (s, 1H), 7.19 (dd, J = 1.6, 8.1 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H) 6.83 (dd, J = 8.1Hz, 1H) 6.04 (s, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.7, 150.8, 147.9, 129.7, 112.8, 112.5, 109.1, 102.1, 96.2, 88.2. HRMS (EI) *m/z* calcd for $C_{10}H_6O_3$ 174.0317, found: 174.0316.

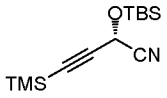
2-Hexyn-1-al (29)



Pyridinium chlorochromate (3.47 g, 1.63 equiv) was dissolved in dry CH_2Cl_2 (35 mL) at 0 °C. To this solution, silica (5.5 g) was added followed by dropwise

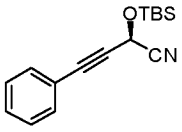
addition of a solution of 2-hexynol (1.00 g, 10.2 mmol) in dry CH_2Cl_2 (3 mL). The reaction temperature was increased to rt and the mixture was stirred for 7h. Then the mixture was filtered over a glass filter and rinsed with pentane. Concentration afforded **29** (411 mg, 42% yield) as a colorless oil. R_f 0.46 (EtOAc/heptane, 1:3). IR (ATR) 2962, 2933, 2872, 2237, 1684, 1273 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.19 (s, 1H), 2.40 (t, 7.0 Hz, 2H), 1.68-1.59 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 177.5, 99.4, 92.4, 21.3, 20.8, 13.6. HRMS (CI) *m/z* calcd for C_6H_9O $(M+H)^+$ 97.0654 found: 97.0651. Data in agreement with literature.[28]

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(trimethylsilyl)but-3-ynenitrile (31)



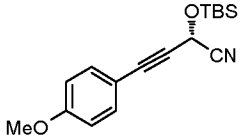
A solution of commercially available 3-trimethylsilylpropynal **23** (2.00 g, 15.8 mmol) in MTBE (15 mL) was added to a cooled (0 °C) solution of KCN (10.3 g, 158 mmol, 10.0 equiv) in citrate buffer (15 mL, pH = 5.0). After addition of (*S*)-HNL (4 mL) the reaction mixture was stirred at 0 °C for 4 h and quenched with 5 M HCl (10 mL) causing the enzyme to precipitate. The precipitate was filtered over a glass funnel filled with cotton. The filtrate was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (150 mL) at 0 °C and TBSCl (2.86 g, 1.2 equiv) and imidazole (2.15 g, 2.0 equiv) were added. After 5 min the reaction was stirred at rt overnight. After quenching with saturated aqueous NH_4Cl the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). Organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified with column chromatography (EtOAc/heptane, 0:1→1:5) to afford **31** (3.51 g, 83% yield) as a colorless oil. R_f 0.73 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +18.7 (*c* 1.03 CH_2Cl_2). ee 99% (chiral GC of THP-protected cyanohydrin, isothermic, 120 °C); $R_{t,1}$ = 13.11 min and $R_{t,2}$ = 14.25 min (*R*). $R_{t,3}$ = 14.67 min and $R_{t,4}$ = 16.57 min (*S*). IR (ATR) 2954, 2924, 2855, 2889, 2358, 2332, 1253, 1101, 1044, 840, 783 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.24 (s, 1H), 0.915 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 116.4, 97.2, 93.5, 52.5, 25.6, 18.2, –0.5, –4.6, –4.5. HRMS (EI) *m/z* calcd for $C_{13}H_{25}NOSi_2$ $(M)^+$: 267.1475, found: 267.1484.

(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-phenylbut-3-ynenitrile (32)



Prepared as described above starting from 3-phenyl-2-propynal **24** (2.42 g, 15.4 mmol) and (*R*)-HNL. Purification by column chromatography (EtOAc/heptane, 0:1→1.5:8.5) afforded **32** (3.60 g, 86% yield) as a yellow oil. R_f 0.69 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ –7.2 (*c* 1.33, CH_2Cl_2). ee 95% (Chiralpak AD-H column: HPLC eluent hexane: *i*PrOH = 85:15, flow 1.0 mL/min); $R_{t,1}$ = 6.12 min (*S*), $R_{t,2}$ = 7.01 min (*R*). IR (ATR) 2958, 2928, 2855, 2228, 2202, 1489, 1256, 1091, 836, 780, 759, 694 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.49-7.46 (m, 2H), 7.42-7.33 (m, 3H), 5.50 (s, 1H), 0.95 (s, 9H), 0.28 (s, 3H), 0.26 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 132.0, 129.7, 128.6, 121.0, 116.5, 87.1, 81.9, 52.7, 25.6, 18.3, –4.6. HRMS (EI) *m/z* calcd for $C_{16}H_{21}NOSi$ 271.1392, found: 271.1394.

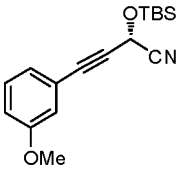
(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(4-methoxyphenyl)but-3-ynenitrile (33)



Prepared as described above starting from 4-ethynylanisole **25** (1.13 g, 6.06 mmol) and (*S*)-HNL. Purification by column chromatography (EtOAc/heptane, 0:1→1.5:8.5) afforded **33** (1.48 g, 81% yield) as a yellow oil. R_f 0.58 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +9.6 (*c* 2.50 CH_2Cl_2). ee >99% (Chiralcel OD-H column: HPLC eluent hexane: *i*PrOH = 80:20, flow 1.0 mL/min); $R_{t,1}$ = 6.41 min (*S*), $R_{t,2}$ = 9.27 min (*R*). IR (ATR) 2954, 2937, 2855, 2229, 1610, 1506, 1290, 1247, 1087, 825, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.42-7.39 (m, 2H), 6.88-6.85 (m, 2H), 5.48 (s, 1H), 3.82 (s, 3H), 0.94 (s, 9H),

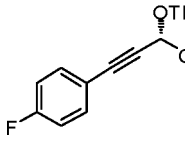
0.27 (s, 3H), 0.25 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 160.7, 133.6, 116.7, 114.3, 113.0, 87.3, 80.7, 55.5, 52.8, 25.6, 18.3, –4.6. HRMS (EI) *m/z* calcd for $C_{17}H_{23}NO_2Si$ 301.1498, found: 301.1493.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(3-methoxyphenyl)but-3-ynenitrile (34)



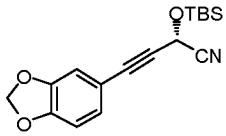
Prepared as described above starting from 3-ethynylanisole **26** (1.10 g, 5.90 mmol) and (*S*)-HNL. Purification by column chromatography (EtOAc/heptane, 0:1→1.5:8.5) afforded **34** (1.42 g, 80% yield) as a yellow oil. R_f 0.63 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +6.7 (*c* 0.60, CH_2Cl_2). ee >99% (Chiralcel OD-H column: HPLC eluent hexane: *i*PrOH = 80:20, flow 1.0 mL/min); $R_{t,1}$ = 6.41 min (*S*), $R_{t,2}$ = 8.68 min (*R*). IR (ATR) 2949, 2932, 2854, 2228, 1597, 1467, 1264, 1100, 841, 776 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28-7.24 (m, 1H), 7.08-7.05 (m, 1H), 6.99-6.98 (m, 1H), 6.96-6.93 (m, 1H), 5.49 (s, 1H), 3.81 (s, 3H), 0.95 (s, 9H), 0.28 (s, 3H), 0.25 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 159.5, 129.7, 124.5, 122.0, 116.9, 116.5, 116.2, 87.0, 81.6, 55.5, 52.7, 25.6, 18.3, –4.6. HRMS (EI) *m/z* calcd for $C_{17}H_{23}NO_2Si$ 301.1498, found: 301.1502.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(4-fluorophenyl)but-3-ynenitrile (35)



Prepared as described above starting from 1-ethynyl-4-fluorobenzene **27** (1.00 g, 3.53 mmol) and (*S*)-HNL. Purification by column chromatography (EtOAc/heptane, 0:1→1.5:8.5) afforded **35** (334 mg, 20% yield) as a yellow oil. R_f 0.61 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +9.3 (*c* 2.57, CH_2Cl_2). ee 93% (Chiralcel OD-H column: HPLC eluent hexane: *i*PrOH = 90:10, flow 1.0 mL/min); $R_{t,1}$ = 7.97 min (*S*), $R_{t,2}$ = 9.23 min (*R*). IR (ATR) 2954, 2928, 2859, 2236, 1510, 1230, 1096, 1005, 832, 776 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.48-7.43 (m, 2H), 7.08-7.02 (m, 2H), 5.48 (s, 1H), 0.95 (s, 9H), 0.27 (s, 3H), 0.25 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 163.4 (d, *J* = 251.6 Hz), 134.1 (d, *J* = 8.6 Hz), 117.1 (d, *J* = 3.4 Hz), 116.4, 116.0 (d, *J* = 22.2 Hz), 86.0, 81.7, 52.7, 25.6, 18.3, –4.6. HRMS (EI) *m/z* calcd for $C_{16}H_{20}FNOSi$ 289.1298, found: 289.1298.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(3,4-methylenedioxyphenyl)but-3-ynenitrile (36)

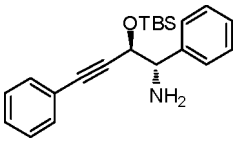


Prepared as described above starting from aldehyde **28** (710 mg, 3.53 mmol) and (*S*)-HNL. Purification by column chromatography (EtOAc/heptane, 0:1→1.5:8.5) afforded **36** (1.03 g, 92% yield) as a yellow oil. R_f 0.58 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +28.9 (*c* 0.27, CH_2Cl_2). ee >99% (Chiralcel OD-H column: HPLC eluent hexane: *i*PrOH = 80:20, flow 1.0 mL/min); $R_{t,1}$ = 7.00 min (*S*), $R_{t,2}$ = 8.74 min (*R*). IR (ATR) 2959, 2923, 2889, 2863, 2228, 1485, 1446, 1247, 1208, 1092, 1031, 836, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.00 (dd,*J* = 1.6, 8.0 Hz, 1H), 6.90 (d, *J* = 1.6 Hz, 1H), 6.77 (d, *J* = 8.0, 1H) 6.00 (s, 2H), 5.46 (s, 1H),0.94 (s, 9H), 0.26 (s, 3H), 0.24 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 149.1, 147.7, 127.1, 116.6, 114.1, 111.8, 108.8, 101.7, 87.2, 80.4, 52.8, 25.6, 18.3, –4.6. HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_3Si$ 315.1291, found: 315.1293.

General procedure for the preparation of $Zn(BH_4)_2$

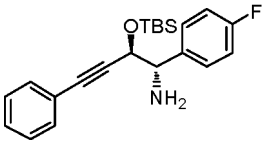
In a typical procedure, a flame dried Schlenk tube was charged with a suspension of dry $ZnCl_2$ (5.0 equiv compared to s.m.) and $NaBH_4$ (5.5 equiv) in a THF/Et_2O mixture (1:1, 0.5 M solution) which was stirred for 16 h at rt.[29] The clear supernatant was used as such.

(1*S*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,4-diphenylbut-3-yn-1-amine (38)



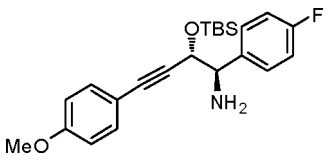
To a solution of cyanohydrin **32** (1.00 g, 3.68 mmol) in dry Et_2O (37 mL) was added dropwise PhMgBr (3.68 mL of a 3.0 M solution in diethyl ether, 3.0 equiv) at 0 °C. After 5 min the reaction mixture was allowed to stir at rt for 2 h. Then dry MeOH (15 mL) was added and the reaction mixture was cooled to –78 °C, A solution of freshly prepared $Zn(BH_4)_2$ (*vide supra*) was added dropwise in 30 min and the reaction mixture was stirred overnight. Then the mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the product was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/heptane, 0:1→3:7) to afford **38** (742 mg, 58% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:8). *Major diastereoisomer*: R_f 0.34 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ –12.4 (*c* 1.71, CH_2Cl_2). IR (ATR) 3031, 2957, 2922, 2850, 1666, 1593, 1493, 1359, 1251, 1091, 836, 788, 758, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44-7.27 (m, 10H), 4.61 (d, *J* = 5.9 Hz, 1H), 4.10 (d, *J* = 5.9 Hz, 1H), 1.99 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 141.5 131.7, 128.5, 128.4, 128.2, 127.7, 127.6, 122.9, 88.6, 86.4, 69.9, 61.5, 29.9, 25.9, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{30}NOSi$ $(M+H)^+$ 352.2097 found: 352.2086.

(1*S*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-fluorophenyl)-4-phenylbut-3-yn-1-amine (39)



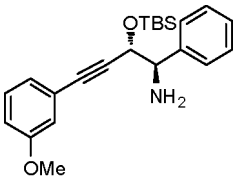
Prepared as described above starting from cyanohydrin **32** (1.00 g, 3.68 mmol) and *p*-FC_6H_4MgBr (5.53 mL of a 2.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→3:7) afforded **39** (772 mg, 57% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:7). *Major diastereoisomer*: R_f 0.19 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ –8.4 (*c* 0.96, CH_2Cl_2). IR (ATR) 3381, 3053, 2959, 2928, 2850, 2224, 1506, 1256, 1217, 1095, 832, 776, 754, 694 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.43-7.28 (m, 7H), 7.05-7.00 (m, 2H), 4.56 (d, *J* = 6.0 Hz), 4.08 (d, 6.0 Hz), 1.78 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.3 (d, *J* = 245.3 Hz), 137.3 (d, *J* = 2.3 Hz), 131.6, 129.3 (d, *J* = 7.9 Hz), 128.5, 128.4, 122.7, 114.9 (d, *J* = 21.2 Hz), 88.4, 86.5, 69.7, 60.7, 25.8, 18.3, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{29}FNOSi$ $(M+H)^+$ 370.2002 found: 370.1997.

(1*R*,2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-fluorophenyl)-4-(4-methoxyphenyl)but-3-yn-1-amine (42)



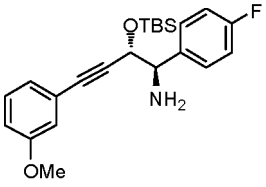
Prepared as described above starting from cyanohydrin **33** (417 mg, 1.38 mmol) and *p*-FC_6H_4MgBr (2.00 mL of a 2.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→1:1) afforded **42** (229 mg, 42% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:30). *Major diastereoisomer*: R_f 0.24 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +13.5 (*c* 0.29, CH_2Cl_2). IR (ATR) 2954, 2932, 2850, 2228, 1610, 1511, 1251, 1221, 1091, 828 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.42-7.38 (m, 2H) 7.33-7.29 (m, 2H), 7.04-7.02 (m, 2H), 6.84-6.81 (m, 2H), 4.55 (d, *J* = 6.0 Hz, 1H), 4.06 (d, *J* = 5.9 Hz, 1H), 3.80 (s, 3H), 2.01 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.4 (d, *J* = 245.2 Hz), 159.8, 137.4, 133.1, 129.3 (d, *J* = 7.9 Hz), 115.0, 114.9 (d, *J* = 21.2 Hz), 114.1, 87.0, 86.5, 69.8, 60.8, 55.4, 25.9, 18.3, –4.58, –5.09. HRMS (ESI) *m/z* calcd for $C_{23}H_{31}FNO_2Si$ $(M+H)^+$ 400.2108 found: 400.2100.

(1*R*,2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(3-methoxyphenyl)-1-phenylbut-3-yn-1-amine (46)



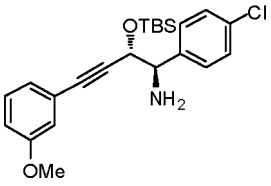
Prepared as described above starting from cyanohydrin **34** (305 mg, 1.01 mmol) and PhMgBr (1.01 mL of a 3.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded **46** (204 mg, 53% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:6). *Major diastereoisomer*: R_f 0.26 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +9.2 (*c* 0.72, CH_2Cl_2). IR (ATR) 2950, 2924, 2855, 1606, 1489, 1286, 1247, 1091, 841, 780, 612 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.29-7.26 (m, 1H), 7.23-7.18 (m, 1H), 6.99-6.96 (m, 1H), 6.92-6.83 (m, 2H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.09 (d, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 1.77 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 141.6, 129.5, 128.2, 127.8, 127.6, 124.2, 123.9, 116.7, 114.9, 88.5, 86.3, 69.9, 61.5, 55.4, 25.9, 18.4, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{23}H_{32}NO_2Si$ $(M+H)^+$ 382.2202 found: 382.2193.

(1*R*,2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-fluorophenyl)-4-(3-methoxyphenyl)but-3-yn-1-amine (47)



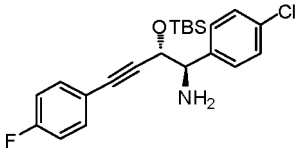
Prepared as described above starting from cyanohydrin **34** (654 mg, 2.17 mmol) and *p*-FC_6H_4MgBr (3.25 mL of a 2.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→1:1) afforded **47** (635 mg, 73% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:7). *Major diastereoisomer*: R_f 0.17 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +15.4 (*c* 0.20, CH_2Cl_2). IR (ATR) 2963, 2924, 2855, 1601, 1511, 1092, 841, 780, 685 cm^{-1}. ^1H-NMR ($CDCl_3$, 400 MHz) δ 7.42-7.37 (m, 2H), 7.23-7.19 (m, 1H), 7.05-7.00 (m, 2H), 6.99-6.96 (m, 1H), 6.90-6.86 (m, 2H), 4.55 (d, *J* = 6.0, 1H), 4.08 (d, *J* = 6.0, 1H), 3.79 (s, 3H), 1.80 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.4 (d, *J* = 245.2 Hz), 159.4, 137.4, 129.5, 129.3 (d, *J* = 7.9 Hz), 124.2, 123.8, 116.8, 115.0 (d, *J* = 21.1 Hz), 114.9, 88.3, 86.4, 69.7, 60.8, 55.4, 25.9, 18.3, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{23}H_{31}FNO_2Si$ $(M+H)^+$ 400.2108 found: 400.2095.

(1*R*,2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-chlorophenyl)-4-(3-methoxyphenyl)but-3-yn-1-amine (49)



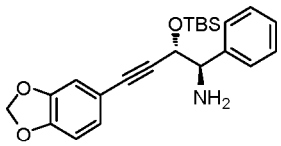
Prepared as described above starting from cyanohydrin **34** (398 mg, 1.32 mmol) and *p*-ClC_6H_4MgBr (3.96 mL of a 1.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded **49** (362 mg, 66% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:6). *Major diastereoisomer*: R_f 0.56 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +16.1 (*c* 0.38, CH_2CL_2). IR (ATR) 2950, 2924, 2855, 1606, 1489, 1286, 1247, 1091, 841, 780, 612 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.30 (m, 4H), 7.24-7.18 (m, 1H), 6.98-6.95 (m, 1H), 6.92-6.85 (m, 2H), 4.57 (d, *J* = 5.8 Hz, 1H), 4.07 (d, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 1.77 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 140.1, 133.3, 129.5, 129.2, 128.3, 124.2, 123.7, 116.7, 115.0, 88.1, 86.5, 69.6, 60.8, 55.4, 25.9, 18.3, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{23}H_{31}ClNO_2Si$ $(M+H)^+$ 416.1813 found: 416.1803.

(1*R*,2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-chlorophenyl)-4-(4-fluorophenyl)but-3-yn-1-amine (50)



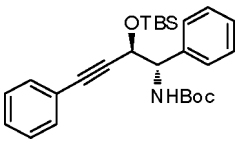
Prepared as described above starting from cyanohydrin **35** (159 mg, 0.549 mmol) and *p*-ClC_6H_4MgBr (1.65 mL of a 1.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→3:2) afforded **50** (123 mg, 56%) as a yellow oil and as an inseparable mixture of diastereoisomers (1:5). *Major diastereoisomer*: R_f 0.22 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +12.5 (*c* 0.24, CH_2Cl_2). IR (ATR) 2950, 2924, 2855, 1601, 1502, 1226, 1100, 837, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.28 (m, 6H), 7.02-6.96 (m, 2H), 4.56 (d, *J* = 5.8 Hz, 1H), 4.07 (d, *J* = 5.8 Hz, 1H), 1.81 (bs, 2H), 0.86 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.7 (d, *J* = 249.8 Hz), 140.1, 133.6, (d, *J* = 8.4 Hz), 133.3, 129.2, 129.1, 128.3, 115.8 (d, *J* = 22.1 Hz), 88.0, 85.5, 69.5, 60.8, 25.9, 18.3, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{28}ClFNOSi$ $(M+H)^+$ 404.1613 found: 404.1607.

(1*R*,2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(3,4-methylenedioxyphenyl)-1-phenylbut-3-yn-1-amine (51)



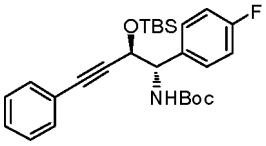
Prepared as described above starting from cyanohydrin **36** (201 mg, 0.637 mmol) and PhMgBr (0.63 mL of a 3.0 M solution in diethyl ether, 3.0 equiv). Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded **51** (173 mg, 69% yield) as a yellow oil and as an inseparable mixture of diastereoisomers (1:7). *Major diastereoisomer*: R_f 0.24 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +11.2 (*c* 0.13, CH_2Cl_2). IR (ATR) 3067, 2954, 2933, 2850, 2220, 1489, 1247, 1213, 1092, 1035, 832, 780, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.43-7.40 (m, 2H), 7.35-7.31 (m, 2H), 7.29-7.26 (m, 1H), 6.90 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 2H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.07 (d, *J* = 5.9 Hz, 1H), 1.83 (bs, 2H), 0.85 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 148.1, 147.5, 141.6, 128.2, 127.7, 127.6, 126.3, 116.2, 111.7, 108.5, 101.4, 86.9, 86.2, 69.9, 61.4, 25.9, 18.4, –4.6, –5.1. HRMS (ESI) *m/z* calcd for $C_{23}H_{30}NO_3Si$ $(M+H)^+$ 396.1995 found: 396.1987.

***tert*-Butyl {(1*S*,2*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1,4-diphenylbut-3-ynyl}carbamate (52)**



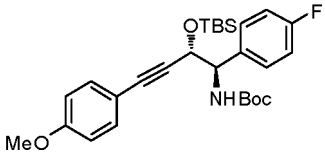
To a solution of amino alcohol **38** (400 mg, 1.14 mmol) in dioxane/H_2O (1:1, 11 mL) were added $NaHCO_3$ (134 mg, 1.2 equiv) and $(Boc)_2O$ (348 mg, 1.2 equiv) and the reaction mixture was stirred for 2 h at rt. After evaporation of dioxane, EtOAc (20 mL) was added. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was purified by column chromatography (EtOAc/heptane, 0:1→1:4) to afford **52** (374 mg, 73% yield) as a white solid and as an inseparable mixture of diastereoisomers (1:17). *Major diastereoisomer*: R_f 0.65 (EtOAc/heptane, 1:3). Mp 116.2 °C. $[\alpha]_D^{20}$ –27.4 (*c* 0.59, CH_2Cl_2). IR (ATR) 3434, 3351, 2954, 2928, 2850, 2358, 1718, 1493, 1359, 1247, 1169, , 1100, 836, 776, 754, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.41-7.39 (m, 2H), 7.35-7.24 (m, 8H), 5.37-5.32 (m, 1H), 4.92-4.87 (m, 2H), 1.43 (s, 9H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 155.5, 138.8, 131.6, 128.6, 128.4, 128.1, 128.0, 127.7, 122.6, 87.4, 87.1, 79.7, 67.0, 59.8, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{27}H_{38}NO_3Si$ $(M+H)^+$ 452.2621, found: 452.2613.

tert-Butyl {(1*S*,2*R*)-2-[(_tert_-butyldimethylsilyl)oxy]-1-(4-fluorophenyl)-4-phenylbut-3-ynyl}carbamate (53)



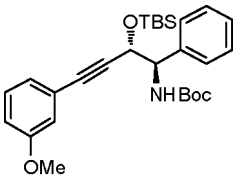
Prepared as described above starting from amino alcohol **39** (400 mg, 1.08 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:4) afforded **53** (367 mg, 72% yield) as a yellow solid and as an inseparable mixture of diastereoisomers (1:10). *Major diastereoisomer*: R_f 0.62 (EtOAc/heptane, 1:3). Mp 112.4 °C. $[\alpha]_D^{20}$ –28.8 (*c* 0.99, CH_2Cl_2). IR (ATR) 2959, 2924, 2855, 1710, 1511, 1485, 1256, 1221, 1161, 1100, 837 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39-7.27 (m, 7H), 7.05-6.99 (m, 2H), 5.34-5.29 (m, 1H), 4.88-4.85 (m, 2H), 1.43 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.4 (d, *J* = 245.3 Hz), 155.3, 134.6, 131.6, 129.6 (d, *J* = 8.0 Hz), 128.7, 128.4, 122.5, 114.9 (d, *J* = 21.4 Hz), 87.2, 79.9, 66.8, 59.2, 53.6, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{27}H_{37}FNO_3Si$ $(M+H)^+$ 470.2527, found: 470.2520.

tert-Butyl {(1*R*,2*S*)-2-[(_tert_-butyldimethylsilyl)oxy]-1-(4-fluorophenyl)-4-(4-methoxyphenyl)but-3-ynyl}carbamate (56)



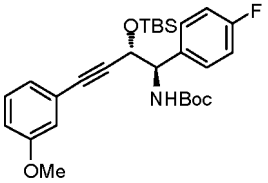
Prepared as described above starting from amino alcohol **42** (210 mg, 0.526 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:4) afforded **56** (184 mg, 70%) as a white solid and as an inseparable mixture of diastereoisomers (1:60). *Major diastereoisomer*: R_f 0.59 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +36.6 (*c* 0.75, CH_2Cl_2). IR (ATR) 3438, 3335, 2963, 2924, 2850, 2232, 1722, 1511, 1251, 1165, 1091, 828, 776 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.35 (m, 2H), 7.23-7.21 (m, 2H), 7.03-6.99 (m, 2H), 6.83-6.80 (m, 2H), 5.33-5.31 (m, 1H), 4.87-4.82 (m, 2H), 3.80 (s, 3H), 1.42 (s, 9H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 164.0, 162.0 (d, *J* = 309.2 Hz), 155.4, 133.1, 132.4, 129.6 (d, *J* = 8.1 Hz), 119.7, 114.9 (d, *J* = 21.1 Hz), 114.1, 87.4, 85.8, 79.9, 66.9, 59.2, 55.5, 28.5, 26.0, 18.4, –4.3, –4.9. HRMS (ESI) *m/z* calcd for $C_{28}H_{39}FNO_4Si$ $(M+H)^+$ 500.2632, found: 500.2937.

tert-Butyl {(1*R*,2*S*)-2-[(_tert_-butyldimethylsilyl)oxy]-4-(3-methoxyphenyl)-1-phenylbut-3-yn-1-yl}-carbamate (60)



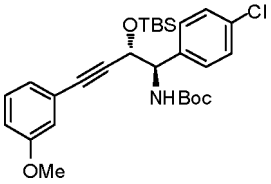
Prepared as described above starting from amino alcohol **46** (200 mg, 0.524 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded **60** (189 mg, 75% yield) as a yellow solid and as an inseparable mixture of diastereoisomers (1:6). *Major diastereoisomer*: R_f 0.56 (EtOAc/heptane, 1:3). Mp 64.5 °C. $[\alpha]_D^{20}$ +27.3 (*c* 0.62, CH_2Cl_2). IR (ATR) 2954, 2921, 2859, 2232, 1714, 1489, 1286, 1160, 1087, 910, 845, 776, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.28 (m, 5H), 7.22-7.17 (m, 1H), 6.91-6.85 (m, 2H), 6.80-6.78 (m, 1H), 5.36-5.29 (m, 1H), 4.87-4.84 (m, 2H), 3.78 (s, 3H), 1.42 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 155.3, 133.5, 129.5, 129.5, 128.7, 128.2, 124.1, 123.4, 116.7, 115.1, 86.9, 80.0, 66.6, 59.2, 55.4, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{28}H_{40}NO_4Si$ $(M+H)^+$ 482.2727 found: 482.2726.

tert-Butyl {(1*R*,2*S*)-2-[(_tert_-butyldimethylsilyl)oxy]-1-(4-fluorophenyl)-4-(3-methoxyphenyl)but-3-ynyl}carbamate (61)



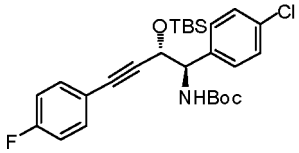
Prepared as described above starting from amino alcohol **47** (595 mg, 1.49 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:4) afforded **61** (597 mg, 80% yield) as a yellow solid and as an inseparable mixture of diastereoisomers (1:12). *Major diastereoisomer*: R_f 0.60 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +27.1 (*c* 0.28, CH_2Cl_2). IR (ATR) 3451, 3334, 2954, 2928, 2854, 1718, 1506, 1489, 1298, 1225, 1164, 841, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39-7.35 (m, 2H), 7.21-7.17 (m, 1H), 7.04-6.99 (m, 2H), 6.89-6.85 (m, 2H), 6.80-6.79 (m, 1H), 5.35-5.30 (m, 1H), 4.89-4.83 (m, 2H), 3.78 (s, 3H), 1.42 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.5 (d, *J* = 245.4 Hz), 159.4, 155.4, 137.2, 129.7 (d, *J* = 8.1 Hz), 129.5, 128.7, 124.1, 123.5, 116.7, 115.0, 114.9 (d, *J* = 20.3 Hz), 87.3, 87.1, 80.0, 66.7, 59.1, 55.4, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{28}H_{39}FNO_4Si$ $(M+H)^+$ 500.2632, found: 500.2633.

tert-Butyl {(1*R*,2*S*)-2-[(_tert_-butyldimethylsilyl)oxy]-1-(4-chlorophenyl)-4-(3-methoxyphenyl)but-3-yn-1-yl}carbamate (63)



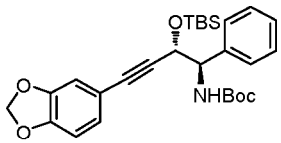
Prepared as described above starting from amino alcohol **49** (201 mg, 0.484 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded **63** (212 mg, 85% yield) as a yellow solid and as an inseparable mixture of diastereoisomers (1:7). *Major diastereoisomer*: R_f 0.49 (EtOAc/heptane, 1:3). Mp 88.9 °C. $[\alpha]_D^{20}$ +28.0 (*c* 0.69, CH_2Cl_2). IR (ATR) 3443, 3330, 2954, 2937, 2859, 1720, 1485, 1282, 1251, 1174, 1091, 1044, 836, 776, 681, 612 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.29 (m, 4H), 7.21-7.17 (m, 1H), 6.90-6.85 (m, 2H), 6.79-6.78 (m, 1H), 5.34-5.30 (m, 1H), 4.88-4.84 (m,2H), 3.78 (s, 3H), 1.42 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 155.3, 133.5, 129.6, 129.5, 128.7, 128.2, 124.1, 123.4, 116.7, 115.1, 87.4, 86.9, 80.0, 66.6, 59.2, 55.4, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{28}H_{39}ClNO_4Si$ $(M+H)^+$ 516.2337 found: 516.2334.

tert-Butyl {(1*R*,2*S*)-2-[(_tert_-butyldimethylsilyl)oxy]-1-(4-chlorophenyl)-4-(4-fluorophenyl)but-3-ynyl}carbamate (64)



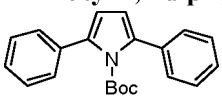
Prepared as described above starting from amino alcohol **50** (111 mg, 0.275 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:4) afforded **64** (109 mg, 79% yield) as a yellow solid and as an inseparable mixture of diastereoisomers (1:5). *Major diastereoisomer*: R_f 0.66 (EtOAc/heptane, 1:3). Mp 108.3 °C. $[\alpha]_D^{20}$ +20.5 (*c* 1.29, CH_2Cl_2). IR (ATR) 3438, 3339, 2954, 2929, 2859, 1714, 1506, 1251, 1234, 1165, 1087, 837, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39-7.24 (m, 6H), 7.03-6.95 (m, 2H), 5.49-5.25 (m, 1H), 4.84-4.71 (m, 2H), 1.43 (s, 9H), 0.92 (s, 9H), 0.14, (s, 3H), 0.13 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.8 (d, *J* = 250.0 Hz), 155.3, 137.3, 133.5 (d, *J* = 8.4 Hz), 129.4, 128.7, 128.2, 118.5, 115.8 (d, *J* = 22.1 Hz), 86.8, 86.3, 80.0, 66.6, 59.2, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{27}H_{36}ClFNO_3Si$ $(M+H)^+$ 504.2137, found: 504.2148.

tert-Butyl {(1*R*,2*S*)-2-[(_tert_-butyldimethylsilyl)oxy]-4-(3,4-methylenedioxyphenyl)-1-phenylbut-3-ynyl}carbamate (65)



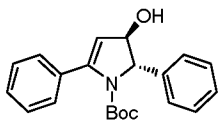
Prepared as described above starting from amino alcohol **51** (146 mg, 0.369 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:4) afforded **65** (135 mg, 74% yield) as a colorless oil and as an inseparable mixture of diastereoisomers (1:8). *Major diastereoisomer*: R_f 0.60 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ +28.9 (*c* 0.27, CH_2Cl_2). IR (ATR) 3434, 2954, 2928, 2855, 2358, 2220, 1723, 1489, 1247, 1161, 1087, 1039, 841, 776, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.38 (m, 2H), 7.34-7.30 (m, 2H), 7.28-7.24 (m, 1H), 6.84-6.80 (m, 1H), 6.74-6.69 (s, 2H), 5.92 (s, 2H), 5.36-5.35 (m, 1H), 4.88-4.84 (m, 2H), 1.42 (s, 9H), 0.92 (s, 9H), 0.12 (s, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 155.4, 148.1, 147.5, 138.8, 128.1, 128.0, 127.7, 126.3, 115.9, 111.6, 108.5, 101.4, 87.0, 85.7, 79.7, 67.0, 59.8, 28.5, 25.9, 18.4, –4.4, –4.9. HRMS (ESI) *m/z* calcd for $C_{28}H_{38}NO_5Si$ $(M+H)^+$ 496.2519, found: 496.2530.

tert-Butyl 2,5-diphenyl-1*H*-pyrrole-1-carboxylate (69)



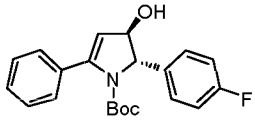
To a solution of carbamate **52** (50 mg, 0.11 mmol) in dry THF (2.0 mL) was added $NaAuCl_4 \cdot 2H_2O$ (4.4 mg, 0.1 equiv) at rt. The reaction temperature was increased to 50 °C and the mixture was stirred for 2h. After cooling to rt, the solvent was removed *in vacuo*. Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded **69** (34 mg, 97% yield) as an off-white solid. R_f 0.88 (EtOAc/heptane, 1:3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.29 (m, 10H), 6.26 (s, 2H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ. 150.0, 136.4, 134.3, 129.0, 128.0, 127.3, 112.3, 84.1, 27.2. Data in agreement with literature.[30]

(4*R*,5*S*)-*N*-_tert_-Butoxycarbonyl-2,5-diphenyl-4-hydroxy-2-pyrroline (71)



To a solution of carbamate **52** (50.0 mg, 0.11 mmol) in dry THF (2 mL) was added dropwise TBAF (110 μL, 1.1 equiv) at 0 °C. The reaction mixture was allowed to reach rt and the mixture was stirred for 1h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with CH_2Cl_2 (10 mL) and the product was extracted from the aqueous layer using CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting colorless oil was dissolved in dry THF (2 mL) and $NaAuCl_4 \cdot 2H_2O$ (4.4 mg, 0.1 equiv) was added at rt. The reaction temperature was increased to 50 °C and the mixture was stirred for 6h. After cooling to rt, Et_3N (10 μL, 5.0 equiv) was added and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) to afford **71** (34 mg, 92% yield) as a yellowish oil. R_f 0.17 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ +22.4 (*c* 0.71, CH_2Cl_2). IR (ATR) 3408, 2980, 2924, 1698, 1636, 1367, 1166, 1018, 752, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.48 (m, 2H), 7.42-7.36 (m, 7H), 7.32-7.26 (m, 1H), 5.34 (dd, *J* = 0.4, 3.3 Hz, 1H), 5.10 (d, *J* = 1.2 Hz, 1H), 4.35 (dd, *J* = 1.2, 3.3 Hz, 1H), 1.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.4, 149.6, 142.5, 135.3, 129.8, 129.5, 128.9, 128.5, 126.3, 112.2, 82.1, 79.5, 74.2, 60.2, 28.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}NO_3$ $(M+H)^+$: 338.1756, found: 338.1769.

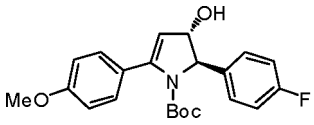
(4*R*,5*S*)-*N*-_tert_-Butoxycarbonyl-5-(4-fluorophenyl)-4-hydroxy-2-phenyl-2-pyrroline (75)



Prepared as described above starting from carbamate **52** (14 mg, 0.03 mmol). Purification by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) afforded **75** (9.0 mg, 88% yield) as a yellowish oil. R_f 0.16 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ +37.6 (*c* 0.62, CH_2Cl_2). IR (ATR)

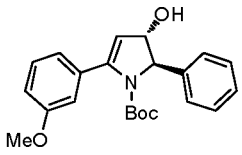
3376, 2980, 1631, 1339, 1143, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50-7.47 (m, 2H), 7.42-7.36 (m, 5H), 7.14-7.08 (m, 2H), 5.35 (dd, *J* = 0.4, 3.3 Hz, 1H), 5.08 (bs, 1H), 4.34 (dd, *J* = 1.2, 3.3 Hz, 1H),1.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ HRMS 161.6 (d, *J* = 243.1 Hz), 154.4, 149.5, 138.6, 135.3, 129.5, 128.9, 128.5, 128.3 (d, *J* = 8.1 Hz), 116.5 (d, *J* = 21.8 Hz), 112.2, 82.2, 79.4, 73.6, 28.1. (ESI) *m/z* calcd for $C_{21}H_{23}FNO_3$ $(M+H)^+$: 356.1662, found: 356.1670.

(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-fluorophenyl)-4-hydroxy-2-(4-methoxyphenyl)-2-pyrroline (76)



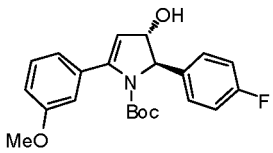
Prepared as described above starting from carbamate **56** (20 mg, 0.04 mmol). Purification by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) afforded **76** (14 mg, 92% yield) as a yellowish oil. R_f 0.19 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ −57.4 (*c* 0.73, CH_2Cl_2). IR (ATR) 3384, 2976, 2928, 2855, 1693, 1671, 1634, 1607, 1508, 1367, 1343, 1249, 1175, 1156, 1031, 833 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.41 (m, 2H), 7.39-7.35 (m, 2H), 7.13-7.08 (m, 2H), 6.97-6.93 (m, 2H), 5.28 (d, *J* = 3.3 Hz, 1H), 5.08 (bs, 1H), 4.30 (dd, *J* = 1.1, 3.3 Hz, 1H), 3.83 (s, 3H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.5 (d, *J* = 244,1 Hz), 161.5, 154.4, 149.3, 138.6, 129.8, 128.2 (d, *J* = 8.1 Hz), 127.5, 116.4 (d, *J* = 21.8 Hz), 114.3, 111.0, 82.1, 79.3, 73.7, 55.8, 28.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{25}FNO_4$ $(M+H)^+$: 386.1768, found: 368.1756.

(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-2-(3-methoxyphenyl)-5-phenyl-2-pyrroline (77)



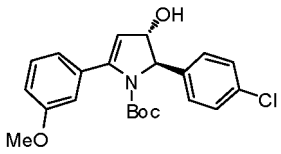
Prepared as described above starting from carbamate **60** (22 mg, 0.05 mmol). Purification by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) afforded **77** (16 mg, 95% yield) as a yellowish oil. R_f 0.16 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ −42.5 (*c* 0.71, CH_2Cl_2). IR (ATR) 3385, 2971, 2924, 1670, 1633, 1335, 1143, 1101, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.26 (m, 6H), 7.10-7.07 (m, 1H), 7.03-7.02 (m, 1H), 6.96-6.93 (m, 1H), 5.36 (d, *J* = 3.3 Hz, 1H), 5.10-5.09 (m, 1H), 4.34 (dd, *J* = 1.2, 3.3 Hz, 1H), 3.83 (s, 3H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.8, 154.3, 149.4, 142.5, 136.6, 130.0, 129.8, 128.5, 126.3, 121.0, 114.8, 114.4, 112.3, 82.1, 79.5, 74.2, 55.8, 28.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NO_4$ $(M+H)^+$: 368.1862, found: 368.1840.

(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-fluorophenyl)-4-hydroxy-2-(3-methoxyphenyl)-2-pyrroline (78)



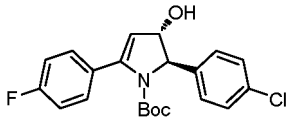
Prepared as described above starting from carbamate **61** (18 mg, 0.04 mmol). Purification by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) afforded **78** (12 mg, 89% yield) as a yellowish oil. R_f 0.17 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ −61.1 (*c* 0.67, CH_2Cl_2). IR (ATR) 3380, 2971, 2924, 1635, 1336, 1223, 1100, 619 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.35 (m, 2H), 7.33-7.29 (m, 1H), 7.15-7.10 (m, 2H), 7.09-7.06 (m, 1H), 7.02-7.01 (m, 1H), 6.96-6.93 (m, 1H), 5.37-5.36 (m, 1H), 5.07 (bs, 1H), 4.32 (dd, *J* = 1.2, 3.3 Hz, 1H), 3.83 (s, 3H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0 (d, *J* = 242.1 Hz), 160.8, 154.3, 149.3, 138.5, 136.5, 130.0, 128.3 (d, *J* = 8.1 Hz), 121.0, 116.5 (d, *J* = 21.8 Hz), 114.8, 114.4, 112.2, 82.2, 79.4, 73.6, 55.8, 28.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{25}FNO_4$ $(M+H)^+$: 386.1768, found: 386.1761.

(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-chlorophenyl)-4-hydroxy-2-(3-methoxyphenyl)-2-pyrroline (79)



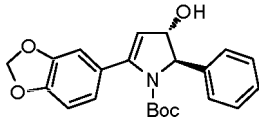
Prepared as described above starting from carbamate **63** (21 mg, 0.04 mmol). Purification by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) afforded **79** (15 mg, 90% yield) as a yellowish oil. R_f 0.18 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ –32.8 (*c* 0.89, CH_2Cl_2). IR (ATR) 3406, 2967, 2928, 1696, 1638, 1601, 1579, 1490, 1366, 1348, 1165, 1145, 1014, 804, 779 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.29 (m, 5H), 7.09-7.06 (m, 1H), 7.02-7.01 (m, 1H), 6.96-6.93 (m, 1H), 5.36 (d, *J* = 3.3 Hz, 1H), 5.07 (bs, 1H), 4.33 (dd, *J* = 1.2, 3.3 Hz, 1H), 3.83 (s, 3H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.8, 154.3, 149.3, 141.3, 136.4, 134.2, 130.0, 129.9, 128.1, 121.0, 114.8, 114.5, 112.2, 82.3, 79.3, 73.6, 55.8, 28.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}ClNO_4Na$ $(M+Na)^+$: 424.1292, found: 424.1310.

(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-5-(4-chlorophenyl)-2-(4-fluorophenyl)-4-hydroxy-2-pyrroline (80)



Prepared as described above starting from carbamate **64** (25 mg, 0.05 mmol). Purification by column chromatography (EtOAc/heptane/Et_3N (1 v/v %, 0:1→1:3) afforded **80** (18 mg, 91% yield) as a yellowish oil. R_f 0.18 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ –47.5 (*c* 0.63, CH_2Cl_2). IR (ATR) 3378, 2980, 2928, 2855, 2488, 2073, 1748, 1698, 1493, 1367, 1144, 1118,974, 837, 793 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.54-7.49 (m, 2H), 7.41-7.34 (m, 4H), 7.16-7.11 (m, 2H), 5.35 (d, *J* = 3.3 Hz, 1H), 5.08 (d, *J* = 0.4 Hz, 1H), 4.33 (dd, *J* = 1.3, 3.3 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.3 (d, *J* = 246.5 Hz), 154.2, 148.3, 141.3, 134.2, 131.4, 130.6 (d, *J* = 8.1 Hz), 129.9, 128.1, 115.7, (d, *J* = 22.1 Hz), 112.4, 82.4, 79.5, 73.7, 28.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{22}ClFNO_3$ $(M+H)^+$: 390.1272, found: 390.1271.

(4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-2-(3,4-methylenedioxyphenyl)-5-phenyl-2-pyrroline (81)



Prepared as described above starting from carbamate **65** (21 mg, 0.04 mmol). Purification by column chromatography (EtOAc/heptanes/1 v/v % Et_3N, 0:1→1:3) afforded **81** (15 mg, 93% yield) as a yellowish oil. R_f 0.19 (EtOAc/heptanes/1 v/v % Et_3N, 1:3). $[\alpha]_D^{20}$ –52.6 (*c* 0.82, CH_2Cl_2). IR (ATR) 3403, 2971, 2932, 2850, 1666, 1633, 1489, 1336, 1101 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.26 (m, 5H), 7.02 (dd, *J* 1.7, 8.0, 1H), 6.96-6.95 (m, 1H), 6.86-6.84 (m, 1H), 5.98 (s, 2H), 5.29 (dd, *J* = 0.4, 3.3 Hz, 1H), 5.08 (bs, 1H), 4.32 (dd, *J* = 1.2, 3.3 Hz, 1H), 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.4, 149.2, 148.7, 142.5, 129.8, 129.6, 129.1, 128.5, 126.3, 122.4, 111.6, 109.1, 108.7, 102.6, 82.1, 79.4, 74.3, 28.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{23}NO_5Na$ $(M+Na)^+$: 404.1474, found: 404.1472.

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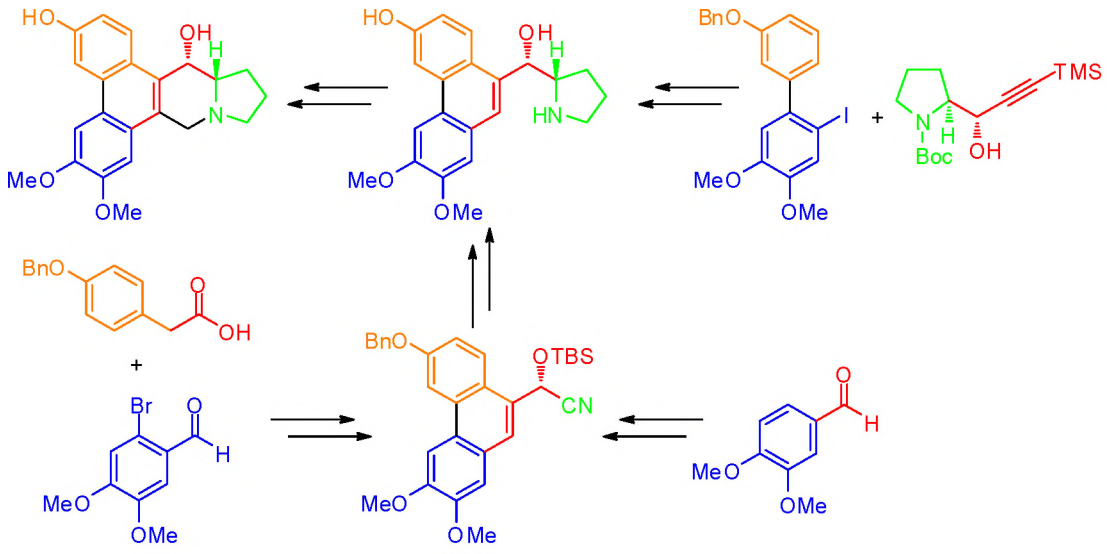
Chapter 4

Towards an Asymmetric Synthesis of an Antitumor Tylophora Alkaloid

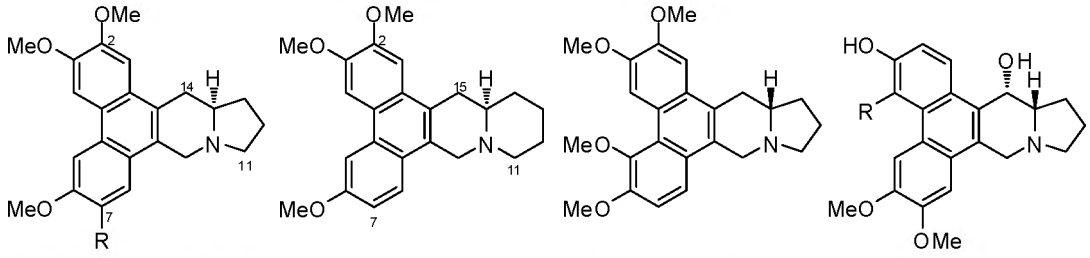


For many years, natural products have served as an inspiration for organic chemists for the development of new synthetic methodologies in organic chemistry.[1] Moreover, natural products are a rich source of compounds displaying interesting bioactivity, which often renders them relevant leads for drug development. In this chapter three approaches toward a potential antitumor phenanthrene-based alkaloid are described making use of the chemistry developed in previous chapters.

4.1 Introduction

Phenanthroindolizidine and phenanthroquinolizidine alkaloids represent a group of pentacyclic natural products isolated mainly from the *Cynanchum*, *Pergularia*, and *Tylophora* species.[2] The leaves of these plants have been used since ancient times for the treatment of various ailments of the respiratory tract such as *i.e.* asthma, bronchitis, and rheumatism. Current research supports this traditional use, demonstrating that extracts from these plants have health benefits including anti-inflammatory, anti-histaminic, and immunomodulatory effects.[3] Most promising, however, is the remarkable cytotoxic activity of many compounds of this class with IC_{50} values in the low nanomolar range.[4] Consequently, since the first isolation of (–)-tylophorine (**1**) in 1935 from the perennial climbing plant *Tylophora indica* native to the plains, hills and forests of southern and eastern India, the class of "tylophora alkaloids" has grown considerably. To date, over sixty compounds have been isolated and characterized, such as (–)-tylophorine (**1**), (–)-antofine (**2**), (–)-cryptopleurine (**3**), and (+)-tylocrebine (**4**) (Figure 4.1).

Figure 4.1 *Representative structures of tylophora alkaloids.*



1 R = OMe; (–)-tylophorine
2 R = H; (–)-antofine

3 (–)-cryptopleurine

4 (+)-tylocrebrine

5 R = H
6 R = OMe

Recently, Wakabayashi *et al.* reported the presence of cytotoxic substances in extracts of the Danaid butterfly *Ideopsis similis*, insects feeding on the leaves of the *Tylophora tanakae*.[5] Soon afterwards, they were able to isolate and identify two cytotoxic substances being a new phenanthroindolizidine alkaloid (**5**), and the already known compound **6**.[6] Since the leaves of *T. tanakae* are known to contain various phenanthroindolizidine alkaloids, compounds **5** and **6** are presumably metabolically converted from such alkaloids in larvae of *I. similis*. During the investigations it was found that both compounds showed IC_{50} values for human gastric cancer cells in the low nanomolar range of 0.5 ng/mL and 0.7 ng/mL, respectively, comparable to

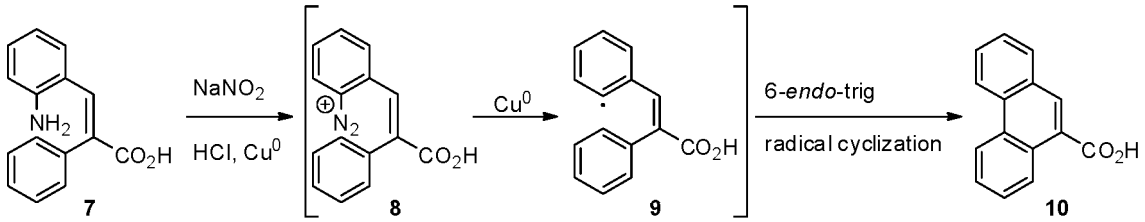
that of clinically employed cytotoxic drugs.[7] Moreover, similar cytotoxic potential was shown with four other cancer cell lines including lung, cervical, colon carcinomas and leukemia. Notably, based upon the NCI's COMPARE[8] analysis, their mode of action appears to be different from other known anticancer compounds.[9]

As can be seen from Figure 4.1, a common structural motif in these pentacyclic natural products is the highly oxygenated phenanthrene ring fused to a saturated nitrogen heterocycle. Previous structure–activity relationships (SAR) of these alkaloids have shown that the rigid phenanthrene structure is required to maintain potent cytotoxicity, and that the lack of an indolizidine ring or the presence of a methyl ether at the 2-position (Figure 4.1) leads to loss of cytotoxicity.[10]

A serious drawback, however, is that in clinical trials these natural alkaloids showed severe central nervous system (CNS) side effects such as ataxia and disorientation thereby prohibiting therapeutic use. Recently, it was suggested that application of more polar derivatives might offset such CNS-toxicity, since such analogues should be less prone to pass the blood–brain barrier.[11] Moreover, tissue specific drug delivery techniques could also be envisaged.[12] From literature it becomes clear that only a few polar antofine analogues with a C-14 hydroxyl group have been synthesized.[10c]

Due to their diverse and potent pharmacological and medicinal properties, the phenantroindolizidines and quinolizidines continue to be targets for synthesis, modification, and determining SAR profiles.[13] Consequently, numerous synthetic routes to these alkaloids have been designed.[14] Since the first publication,[15] the use of the arenediazonium salt **8** to effect intramolecular coupling providing 9-phenanthrenecarboxylic acid **10**, the so-called Pschorr reaction,[16] stands out as the most viable method, followed by intramolecular electrophilic addition (Scheme 4.1).[17] More recent total syntheses are based on the latter methods in combination with key steps such as a chiral auxiliary-mediated asymmetric alkylation,[18] an Overmann rearrangement,[19] an enantioselectively catalyzed intramolecular alkene carboamination,[20] Friedel–Crafts acylation,[21] and enantioselective phase-transfer alkylation.[22]

Scheme 4.1 *Pschorr phenanthrene synthesis.*

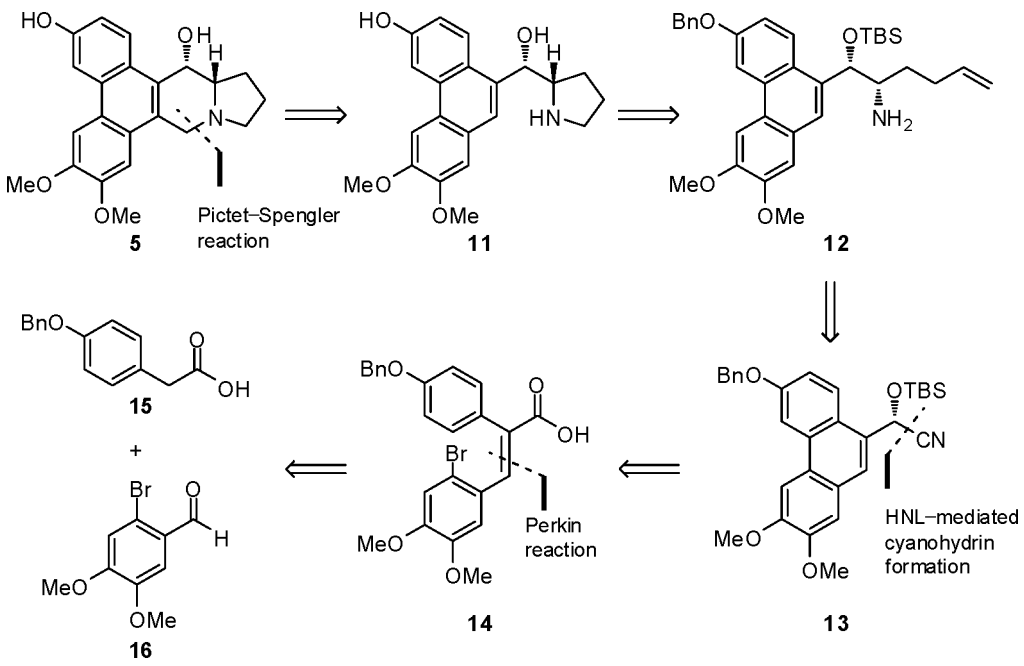


Remarkably, up till now, no total synthesis of (+)-*trans*-3,14α-dihydroxy-6,7-dimethoxy-phenanthroindolizidine (**5**) has been reported. To this end and intrigued by the exquisite structural futures and promising biological profile, we embarked on a project aimed at the development of a novel but flexible approach to compound **5**.

4.2 Retrosynthetic strategy

At the outset, we felt that the pentacyclic skeleton of the target natural products might be constructed by employing a Pictet–Spengler annulation[23] of 2-arylmethylpyrrolidine **11** (Scheme 4.2). The cyclization precursor **11** should be accessible from the *syn*-amino alcohol **12** by sequential ozonolysis, and hydrogenation. The intermediate **12** was in turn envisioned to arise from the enantiopure cyanohydrin **13**, *via* addition of an organometallic reagent and stereoselective reduction. It occurred to us that the cyanohydrin functionality might be introduced by an asymmetric HNL-mediated addition of hydrogen cyanide onto the corresponding aldehyde. Further analysis indicated that the requisite cyanohydrin **13** should be accessible from the readily available bromide **14** obtained *via* a Perkin condensation[24] of fragments **15** and **16**. We were confident that the synthetic methodologies explored in the previous chapters, would be well-suited for application in the aforementioned synthetic plan.

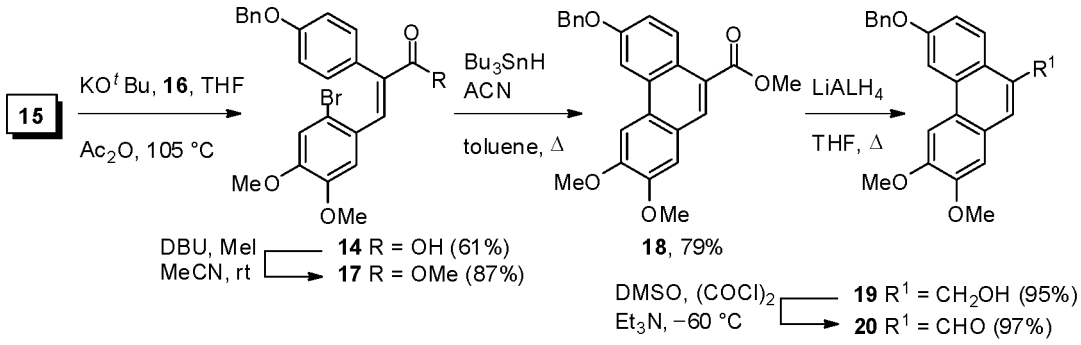
Scheme 4.2 *Retrosynthetic strategy.*



4.3 Synthesis of the phenanthrene-based cyanohydrin

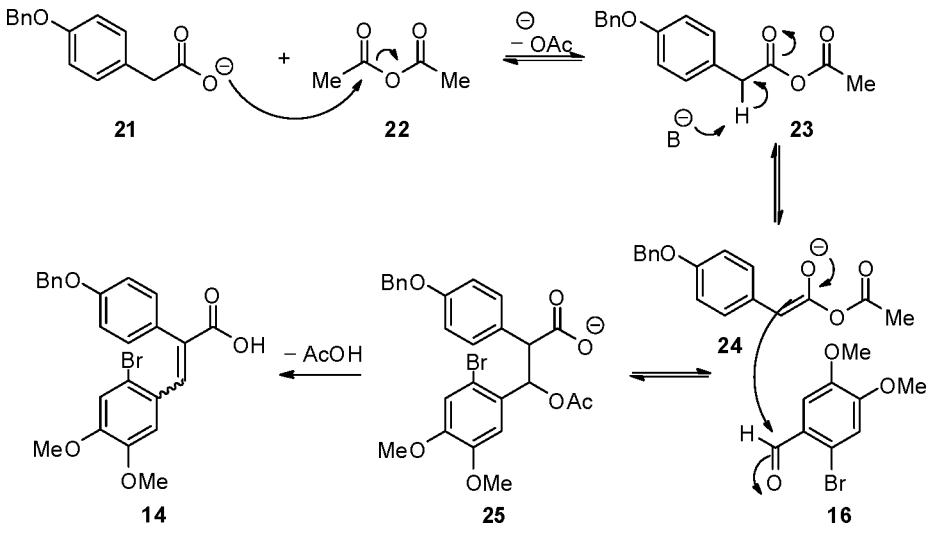
The synthesis of phenanthrene aldehyde **20**, based on a modified Pschorr process, commenced with the Perkin condensation of *in situ* generated potassium 4-benzyloxyphenyl acetate (**21**) and commercially available 2-bromo-4,5-dimethoxybenzaldehyde (**16**) in the presence of Ac_2O (**22**) to yield the bromo-substituted cinnamic acid derivative **14** as single isomer after recrystallization (Scheme 4.3).[25] Esterification of the latter compound **14** using DBU and MeI in acetonitrile provided the corresponding methyl ester **17** in 87% yield. Compound **17** was then subjected to a radical process by treatment with Bu_3SnH in the presence of a catalytic amount of azobis(cyclohexanecarbonitrile) (ACN) in boiling toluene to afford product **18** in a good yield of 79%. Reduction of the ester group with $LiAlH_4$ gave phenanthrenyl methanol **19**, which smoothly underwent a Swern oxidation to yield aldehyde **20**.

Scheme 4.3 *Synthesis of phenanthrene* ***20****.*



Generally, the mechanism of the Perkin transformation starts with addition of the alkali salt of acid **21** to Ac_2O (**22**) (Scheme 4.4). After formation of enolate **23**, aldol condensation takes place, followed by intramolecular acyl transfer. The last step in the mechanism includes E2 elimination providing the cinnamic acid derivative **14** as a mixture of geometric isomers.

Scheme 4.4 *Mechanism of the Perkin condensation.*

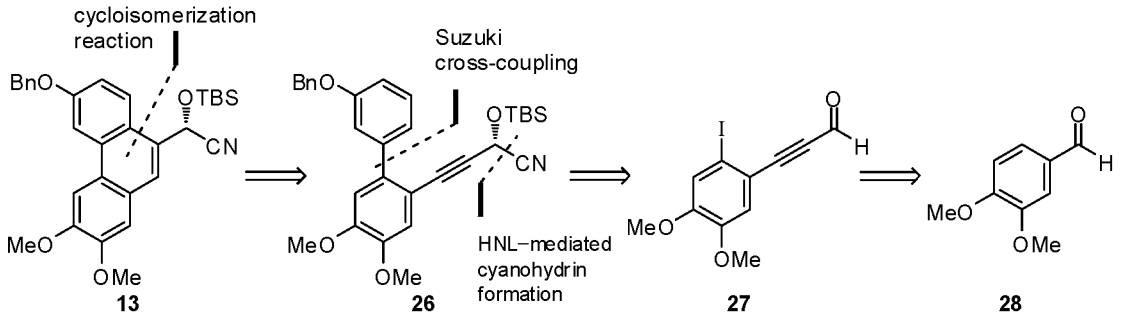


Inspired by the successful enzyme-catalyzed hydrocyanation reactions described in the previous chapters, the proposed key transformation into cyanohydrin **13** was investigated. Unfortunately, subjection of substrate **20** to both (*R*)- and (*S*)-HNL under the known conditions did not afford any reaction at all. A logical explanation for this observation could be that the steric bulk of the aromatic system hinders the substrate from being accepted by the enzyme.

4.4 Revised synthesis of the phenanthrene-based cyanohydrin

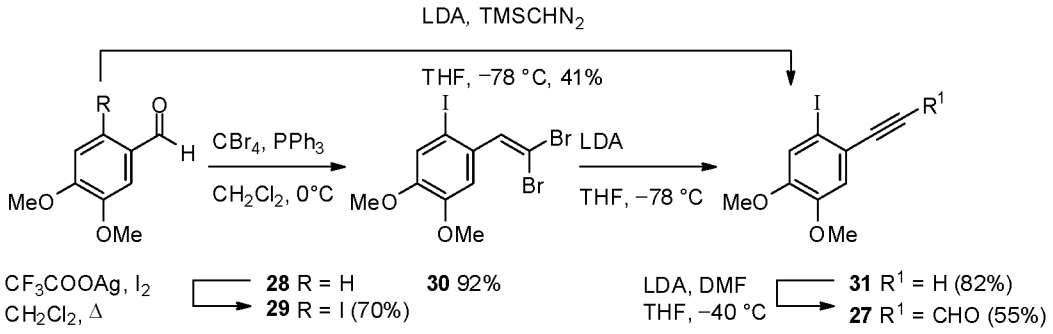
As mentioned above, we were unsuccessful in accessing the phenanthrene cyanohydrin **13** *via* chemoenzymatic cyanohydrin formation. Building on methodology that had already been developed in Chapter 3, the retrosynthetic planning to arrive at key structure **13** was redesigned (Scheme 4.5). Enzymatic studies on acetylene-containing aldehydes revealed that these aldehydes were well accepted by the HNL-enzymes (see: Chapter 3). For this reason we believe that compound **26** could serve as an important building block in the synthesis of the phenanthrene cyanohydrin **13**. Thus, formation of **13** was intended to proceed by transition metal-catalyzed cycloisomerization of *ortho*-alkylated biphenyl **26** which in turn could arise from a Suzuki reaction with a suitably functionalized boronic acid. The acetylenic aldehyde **27** was envisaged to arise from commercially available veratrylaldehyde (**28**).

Scheme 4.5 *Revised synthetic strategy of compound 13.*



Attention was now directed to preparation of the requisite cyanohydrin precursor **27**. Silver trifluoroacetate-mediated iodination of the electron rich aromatic system of **28** delivered the corresponding iodide **29** in fairly good yield (Scheme 4.6). Next, aldehyde **29** was converted in one step into alkyne **31** by reaction with lithio trimethylsilyl diazomethane.[26] The rather modest yield of 41% was attributed to the sensitivity of aldehyde **29** under the reaction conditions. A much improved yield was obtained by applying the Corey–Fuchs protocol[27] allowing for one-carbon elongation of aldehyde **29** to dibromoolefin **30** and consecutive treatment with LDA to afford the terminal alkyne **31** in 75% yield over two steps. The final reaction prior to arrival at the targeted aldehyde structure **27** proceeded by reaction of the lithium acetylide of alkyne **31** with DMF as the formylating agent under the conditions developed by Journet *et al.*[28]

Scheme 4.6 *Synthesis of aldehyde 27.*

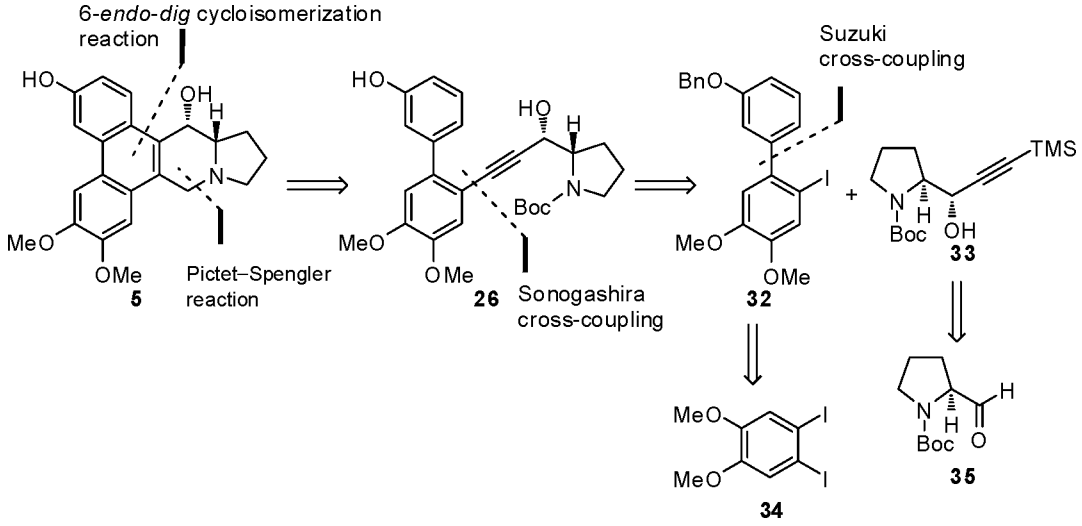


With the acetylenic aldehyde **27** in hand, the stage was set to investigate the HNL-mediated asymmetric hydrogen cyanide addition reaction. Unfortunately, subjection of this compound to the enzymatic hydrocyanation conditions with both enzymes again showed no product formation. We presume that due to the steric bulk of the substituents on the aromatic ring – mainly the iodide– the substrate has become too big for the enzyme. After these unsatisfactory results, we decided to abandon our investigations into the enzyme-based synthesis and focused on an alternative approach which might lead to **5**.

4.5 Stereocontrolled acetylide addition

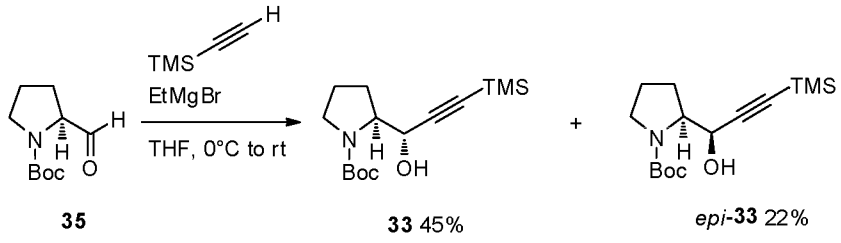
As already pointed out in previous sections, we have encountered severe difficulties in forming the phenanthrene cyanohydrin **13** and therefore chose a non-enzymatic route. The retrosynthetic analysis of **5** is shown in Scheme 4.7. Upon first inspection, it appears that the pentacyclic skeleton of the target natural product could be constructed by employing the known Pictet–Spengler annulation of pyrrolidine **26**, which was previously synthesized *via* a different synthetic route. Fragments **32** and **33** are the basic modules in the synthetic plan as they may serve as precursors ligated *via* a Sonogashira cross-coupling to access **26**. Further analysis indicated that synthesis of fragments **32** and **33** calls for preparation of diiodoveratrole **34** and application of Boc-(*S*)-prolinal **35**.

Scheme 4.7 *Retrosynthetic analysis.*



Our intention was to identify a simple way of accessing each diastereomeric hydroxypyrrolidine **33**, which in principle, would give access to all four diastereoisomers of the target natural product. For the initial study, the stereocontrolled ethynylation of Boc-(*S*)-prolinal **35** with the Grignard reagent prepared from trimethylsilylacetylene was investigated. The two possible products **33** and *epi*-**33** were expected (Scheme 4.8) to be derived either from a chelation-controlled transition state in the case of **33** (1'*S*), or from Felkin–Anh–type attack leading to the (1'*R*)-alcohol *epi*-**33**.

Scheme 4.8 *Diastereoselective magnesium acetylide addition to aldehyde* ***35****.*



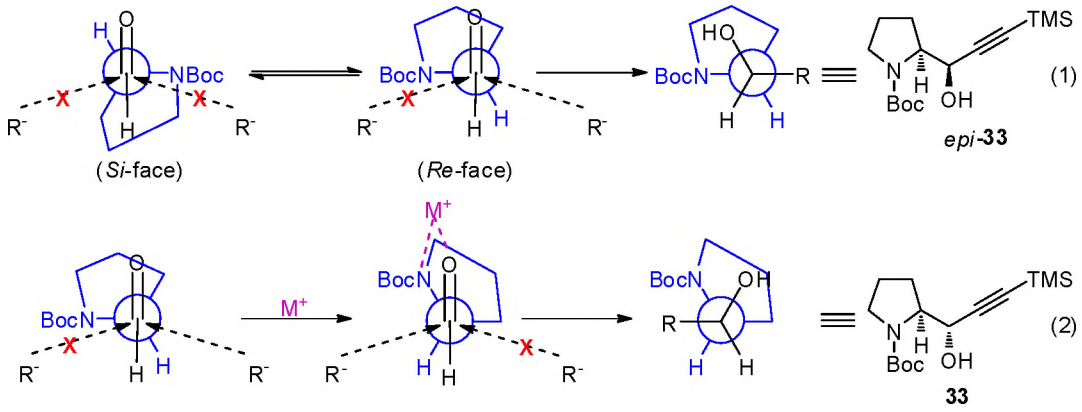
In this first experiment, the magnesium acetylide gave the Boc-protected acetylenic amino alcohol in a 2:1 ratio favoring the desired anti-Felkin–Anh product **33**. However, conversion of aldehyde **35** into the product was accomplished in rather poor stereoselectivity and modest total yield of 67%.[29] The latter result is presumably due to competing enolization leading to regeneration of the aldehyde upon workup. To establish the absolute/relative stereochemistry of products **33** and *epi*-**33**, both diastereoisomers were subjected to high field 2D-NOESY.

Unfortunately however, at this stage of the synthesis we were unable to give a solid assignment of the stereochemistry.

4.6 Explanation of the stereochemical outcome

In case of Felkin–Anh control, the outcome can be explained by looking at the two possible conformers that are involved (Scheme 4.9, equation 1). Nucleophilic attack would take place at the least hindered side (*Re*-face), perpendicular to the carbonyl moiety giving *epi*-**33** as the major diastereoisomer. In our case, introduction of the acetylenic side chain takes place in the opposite direction by chelation control (equation 2). During the stereoinduction, the magnesium ion coordinates to the carbonyl oxygen and the amine nitrogen, enforcing a *syn*-periplanar relationship between the amine and carbonyl groups which leads to the *anti*-diastereomer **33**.

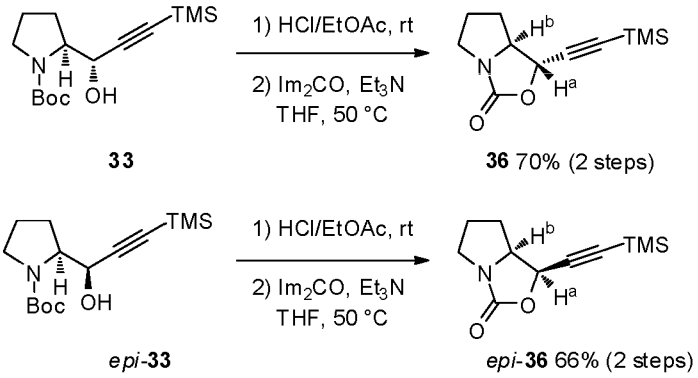
Scheme 4.9 *Rationale for the stereochemical outcome.*



4.7 Elucidation of the diastereochemistry

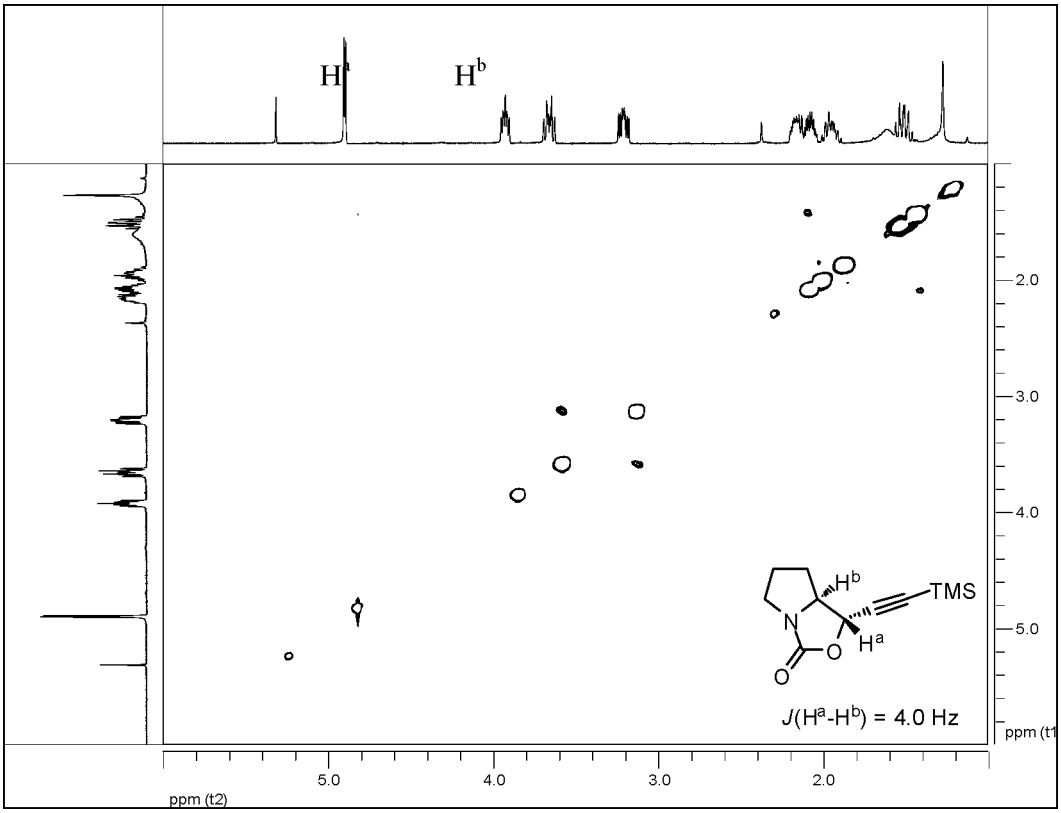
To ascertain the absolute/relative stereochemistry, we decided to convert both diastereoisomers **33** and *epi*-**33** into the corresponding oxazolidinones by two routine operations (Scheme 4.10). Stirring under acidic conditions using a solution of 2M HCl in ethyl acetate allowed for clean removal of the Boc protecting group. Next, the crude products were subjected to 1,1'-carbonyldiimidazole in THF (50 °C) furnishing the desired oxazolidinones **36** and *epi*-**36** in 70% and 66% yield, respectively, over two steps.

Scheme 4.10 *Synthesis of oxazolidinones* ***36*** *and epi-****36****.*



With the cyclized compounds in hand, the stage was set to probe the envisaged high field 2D-NOESY experiments (Figure 4.2). Both ^{1}H-NMR spectra show clear signals and the protons relevant to determine the stereochemistry are easy to distinguish. Inspection of the NOE spectra clearly shows a cross signal between H^a and H^b (marked with a box) in the spectrum of oxazolidinone *epi*-**36** indicating a *cis*-relationship between these protons. The absence of the signal between H^a and H^b in the spectrum of **36** implicates a *trans*-relation. Furthermore, examination of the ^{1}H-NMR spectrum of oxazolidinone *epi*-**36** showed H^a as a doublet located at δ 5.28 with a coupling constant $J(H^a\text{-}H^b)$ of 8.0 Hz while the same signal of the (1*S*)-diastereoisomer oxazolidinone **36** appeared at δ 4.86 with a coupling constant $J(H^a\text{-}H^b)$ of only 4.0 Hz, thereby confirming the aforementioned conclusion. In addition, X-ray structure analysis of the crystals obtained from prolinol derivative **38** (Figure 4.3) unequivocally confirmed the stereochemistry as already evidenced by the 2D-NOESY measurements.

Figure 4.2 *2D-NOESY spectrum of oxazolidinones* ***36*** *and epi-****36****. Cross peaks are boxed.*



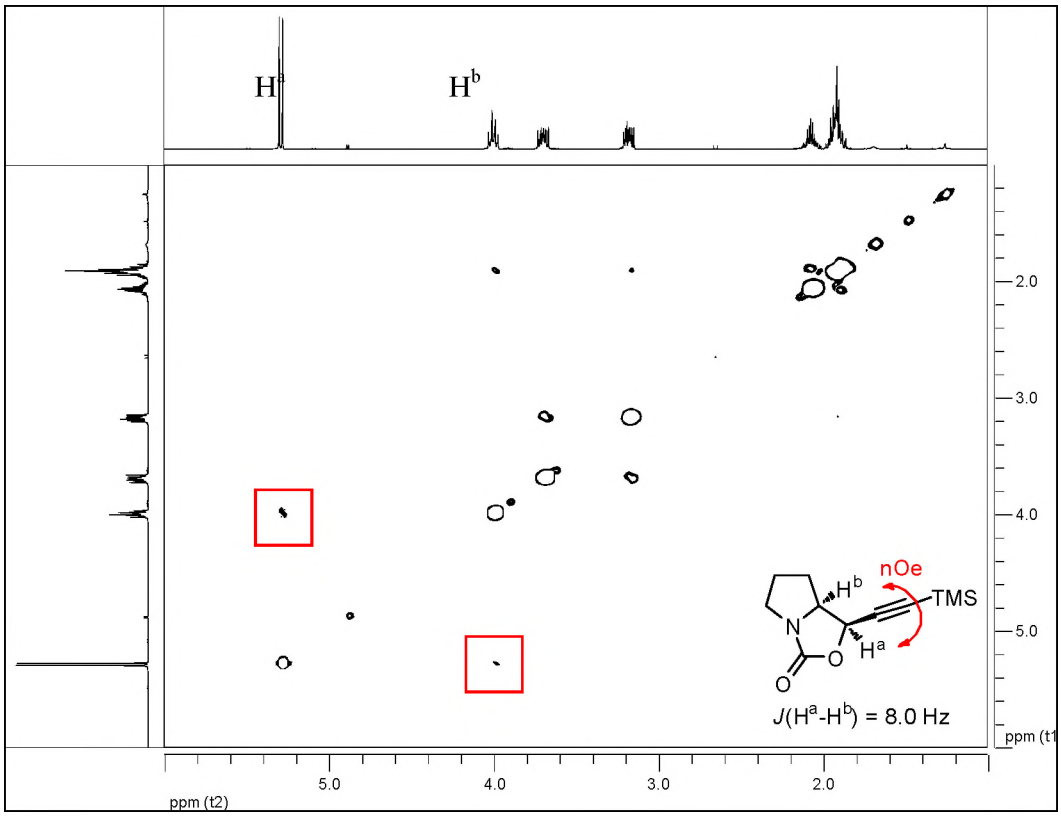
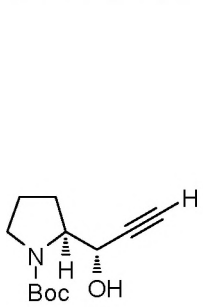
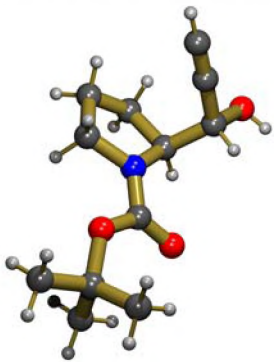


Figure 4.3 *Crystal structure of prolinol derivative* ***38****.*



38

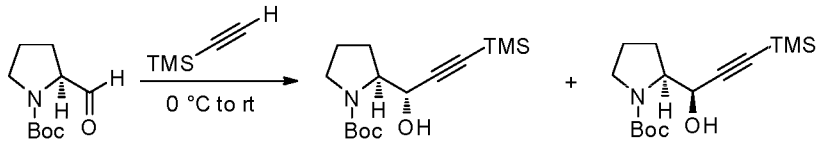


4.8 Diastereoselective acetylide addition

To overcome the rather disappointing results in terms of yield and stereoselectivity, we turned our attention to additional reagent control. Carreira *et al.* have developed an effective method for the diastereocontrolled addition of zinc acetylides to aldehydes employing inexpensive (+)-*N*-methylephedrine as a chiral ligand.[30] We were surprised to find that under these conditions, in our hands we were not able to see any product formation at all (Table 4.1, entry 1). After some unsuccessful variation of reaction conditions (different preparation of $Zn(OTf)_2$ and various bases), a paper by Zhou *et al.* stimulated us to investigate the asymmetric acetylide addition to aldehyde **35** by using 1,1'-bi-2-naphthol (BINOL) in combination with Et_2Zn, $Ti(O^iPr)_4$, and HMPA at room temperature.[31] Gratifyingly, these conditions allowed for clean conversion into product (entry 3). After comparison of the ^{1}H-NMR spectra it was concluded that when (*S*)-BINOL was used, product *epi*-**33** was obtained in 79% yield in a diastereomeric ratio of 1:10. Fortunately, both diastereoismomers could be separated by repeated column chromatography. Subsequently, we also examined the application of (*R*)-BINOL, which would hopefully lead to the formation of the other diastereoisomer **33**. Interestingly, (*R*)-BINOL failed to give the desired isomer **33** but instead led to smooth conversion into *epi*-**33** in a comparable diastereomeric ratio (entry 4). As a test case for the stereoinduction, we also performed the same reaction without the presence of a chiral BINOL auxiliary. When the reaction was setup and allowed to proceed without BINOL, adduct *epi*-**33** was isolated at a much slower rate and in only 54% yield and with a decreased diastereomeric ratio of 1:2.5 (entry 5). Pleasingly, this inherent diastereoselectivity in the undesired Felkin–Anh direction could be overturned by replacement of BINOL and $Ti(O^iPr)_4$ with (+)-*N*-methylephedrine. In the event, the chelation-controlled compound **33**, required for

natural product **5**, was obtained as the major isomer in 82% yield and a diastereomeric ratio of 6.6:1 (entry 6). On the contrary, (–)-*N*-methylephedrine as chiral auxiliary was not able to deliver an acceptable diastereomeric ratio probably due to a mismatched case (entry 7). For the time being, we opted that further fine tuning and optimization of the diastereocontrolled addition reaction onto aldehyde **35** could be performed after completion of the total synthesis.

Table 4.1 *Screening of acetylide addition on aldehyde* ***35****.*



35 **33** ***epi*-33**

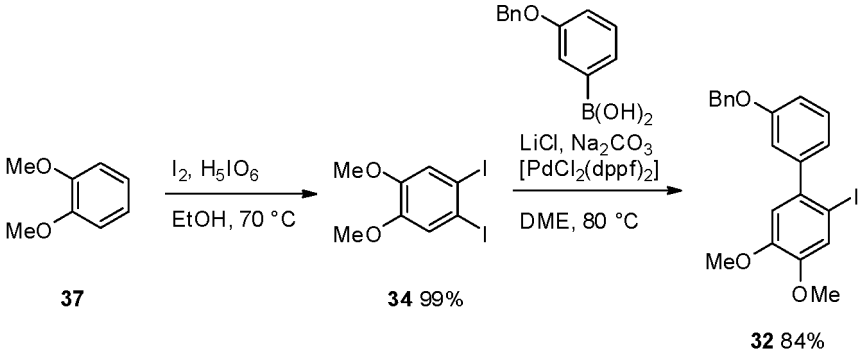
entry	conditions	catalyst	yield (%)[a]	**33**/ *epi*-**33** ratio[b]
1	$Zn(OTf)_2$, Et_3N, toluene	(+)-*N*-methylephedrine	–	–
2	$ZnCl_2$, THF[c]		–	–
3	Et_2Zn, $Ti(O^iPr)_4$, HMPA, CH_2Cl_2	(*S*)-BINOL	79	1:10
4	Et_2Zn, $Ti(O^iPr)_4$, HMPA, CH_2Cl_2	(*R*)-BINOL	80	1:10
5	Et_2Zn, $Ti(O^iPr)_4$, HMPA, CH_2Cl_2	–	54	1:2.5
6	Et_2Zn, HMPA, CH_2Cl_2	(+)-*N*-methylephedrine	82	6.6:1
7	Et_2Zn, HMPA, CH_2Cl_2	(–)-*N*-methylephedrine	80	2.2:1

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H-NMR analysis. [c] A commercially available lithium (trimethylsilyl)acetylide solution in THF (0.5 M) was used.

4.9 Synthesis of the phenanthrene scaffold

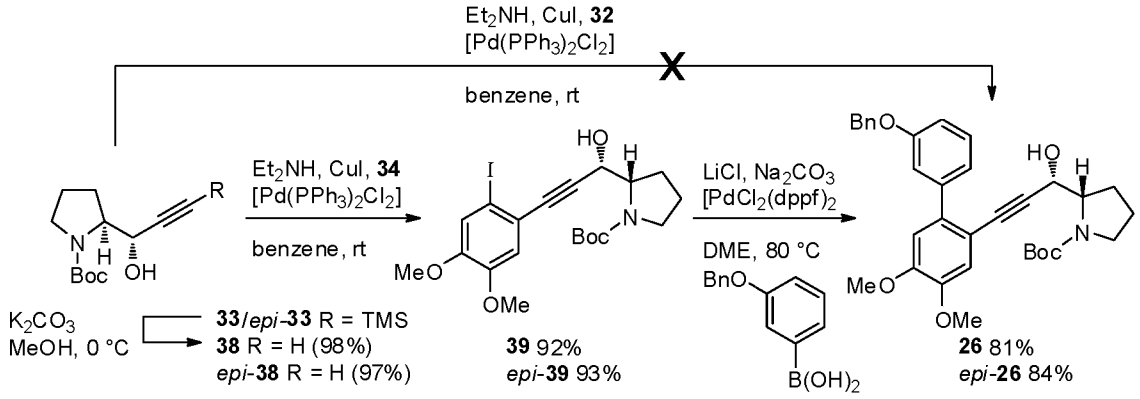
With key intermediate **33** in hand, we turned our attention to the preparation of the biphenyl fragment **32**, which was easily prepared in two steps as shown in Scheme 4.11. Aromatic diiodination provided the desired veratrole derivative **34** in quantitative yield. Standard Suzuki cross-coupling reaction employing commercially available 3-benzyloxyphenyl boronic acid afforded substituted biphenyl iodide **32** in a high yield of 84%.

Scheme 4.11 *Synthesis of fragment 32.*



With multigram quantities of **32** in hand we began the second stage of our synthesis by cleavage of the TMS-protecting group with K_2CO_3 in methanol affording terminal alkyne **38** and its epimer *epi*-**38** in 98 and 97% yield, respectively, after column chromatography (Scheme 4.12). The next step in the assembly process was the coupling of the two fragments **38** and **32** *via* palladium catalysis. Our system turned out to be not reactive enough, however, so that only starting material was recovered. Remarkably, in further experiments this seemingly routine transformation was low yielding or failed to give the desired product at all. Gratifyingly, an alternative route for successful assembly of the fragments was initiated by simply altering the order of steps. Thus, terminal alkyne **38** was first reacted in a Sonogashira cross-coupling in the presence of 5 mol % of $[Pd(PPh_3)_2Cl_2]$ and 20 mol % of CuI to provide product **39** in 92% yield. Suzuki reaction with 3-benzyloxyphenyl boronic acid then constituted the phenanthrene precursor **26** in a good yield of 81%. The reactions with epimer *epi*-**38** delivered *epi*-**26** in comparable yield.

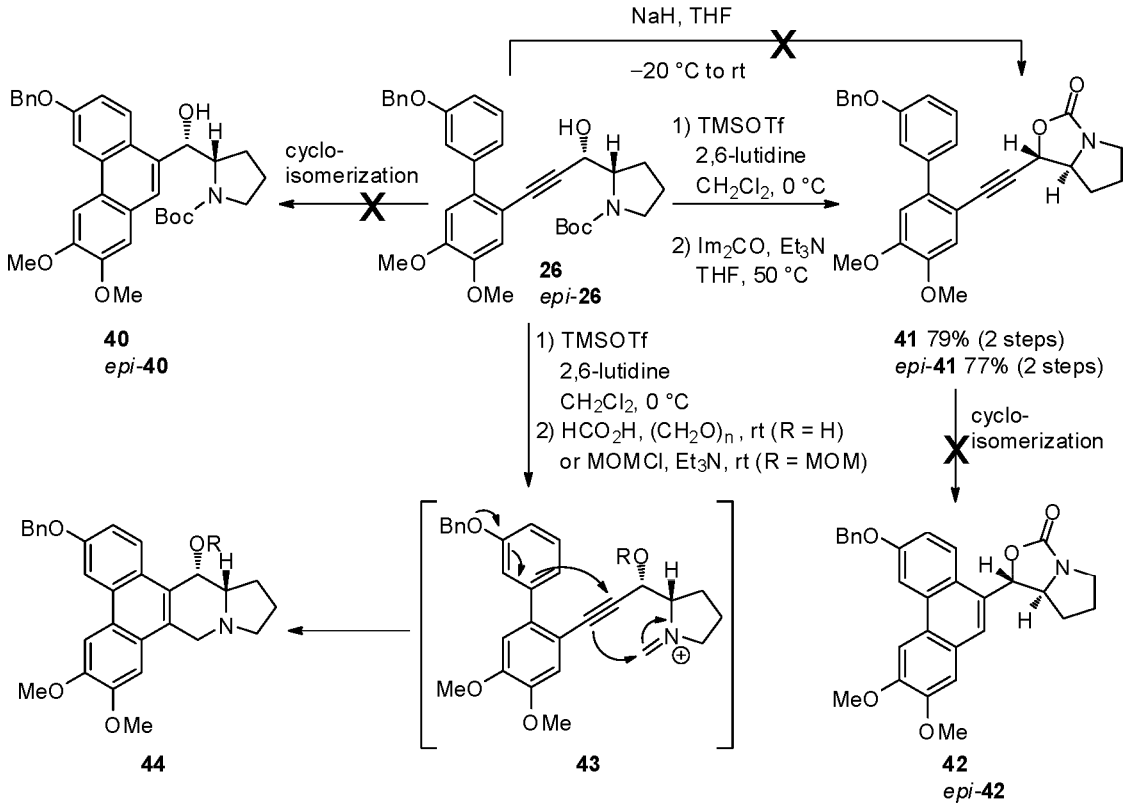
Scheme 4.12 *Synthesis of building block 26.*



The next goal was to investigate the transition metal-catalyzed cycloisomerization. Recent investigations from the Fürstner lab have shown that exposure of biaryl derivatives bearing an alkyne moiety on one of the *ortho*-positions to a variety of carbophilic Lewis acids engenders an efficient 6-*endo*-*dig* cycloisomerization to form polycyclic (hetero)arenes.[32] Interestingly, after numerous experiments of **26** and *epi*-**26** with an assortment of transition metal catalysts and (Brønsted) acids under different experimental conditions, it was becoming clear that this did not lead to the anticipated formation of phenanthrenes **40** and *epi*-**40** (Scheme 4.13). Instead, a complex mixture of products was obtained, from which most likely an elimination product, being the major product, could be identified by mass analysis. All attempts to further analyze or isolate this compound were unsuccessful.

These results led us to believe that the sensitivity of the free hydroxyl at C-14 toward elimination under the conditions applied must be the main reason for preventing success. We were hoping that changing the free hydroxyl in a less good leaving group such as a cyclic carbamate would be more fruitful. In response to this analysis, the convergent route to the cyclization precursors **41** and *epi*-**41** summarized in Scheme 4.13 was designed. Our first attempt to remove the Boc group under acidic conditions using a cold solution of 2M HCl in ethyl acetate failed completely and led to instantaneous product decomposition instead. Luckily, this problem was overcome by conducting the deprotection under particularly mild conditions in the presence of TMSOTf buffered with 2,6-lutidine.[33] After extraction, the crude products were immediately treated with 1,1'-carbonyldiimidazole in heated THF (50 °C) affording the desired compounds **41** and *epi*-**41** in good yield over two steps. Direct oxazolidinone formation by exposure of alcohol **26** to NaH in dry THF was also attempted, but merely led to formation of side products.

Scheme 4.13 *Synthesis of the phenanthrene scaffold.*

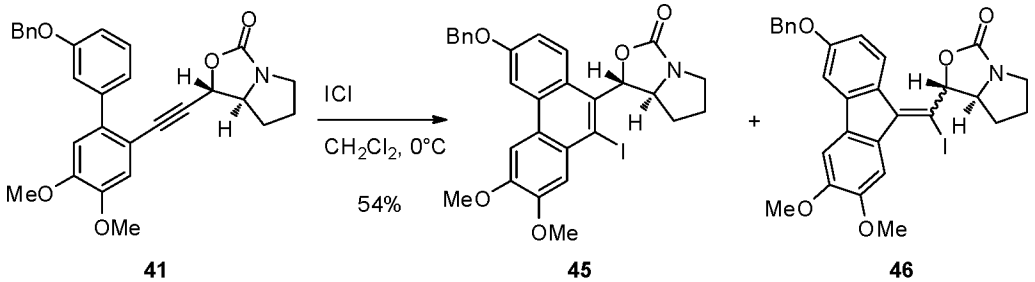


Having both oxazolidinones in hand, the cycloisomerization was investigated. Unfortunately, despite extensive variation of the conditions and catalysts (*vide supra*), we were unable to establish a successful protocol for the transformation into **42** and its epimer *epi*-**42**. The starting compounds **41** were inreactive in all cases and analysis of the reaction mixtures only indentified starting material.

Alternatively, we anticipated that a tandem Pictet–Spengler reaction on deprotected **26** would provide an elegant entry into the final antofine skeleton *via* 6-*endo*-trig cyclization and consecutive attack of the (electron rich) aromatic system on the intermediate cation. Indeed, stirring the free amine at rt in either a formic acid/paraformaldehyde mixture, or in the presence of MOMCl showed the formation of the corresponding *N*-acyliminium ion **43** as could be determined by mass spectrometry analysis of the crude reaction mixtures. However, both the anticipated tandem sequences gave multiple products and, in case of MOMCl, only led to traces of the desired product **44** (R = MOM). Monitoring the reaction in formic acid showed a small amount of addition product being the result of intermolecular attack of formic acid onto the *N*-acyliminium ion **43**.

Among the conditions already used in the cycloisomerization reaction of **26** and *epi*-**26**, we also investigated the possibility of intramolecular cyclization with highly electrophilic sources of iodonium ions, such as $I(py)_2BF_4$, which was first used by Barluenga in the presence of a strong acid to cyclize 1,4-diphenyl-1-butyne to the corresponding iododihydronaphthalene.[34] However, under these conditions complete decomposition took place, most probably due to the strong TfOH that was used. Another way of synthesizing polycyclic aromatic and heteroaromatic compounds was developed by Larock and co-workers.[35] They successfully developed an iodine monochloride (ICl)-induced electrophilic cyclization. A notable feature in this strategy is the preference for 6-*endo*-dig cyclization to give phenanthrenes over the alternative 5-*exo* mode of cyclization. Encouraged by these results, we treated compound **41** with a slight excess of ICl in cold dichloromethane (Scheme 4.14). This route allowed conversion of starting material into a product which upon isolation and ^{1}H-NMR analysis showed a mixture of two inseparable products in a moderate yield of 54% in a 1:3 ratio. ^{1}H-NMR temperature experiments indicated that the two products were no conformational isomers. We therefore assume that this mixture is a result of 6-*endo*-dig and 5-*exo*-dig cyclization. To provide more insight, various mass spectrometry techniques (CI, ESI, MALDI) were utilized for elucidating the molecular mass of the two products. Although CI did show the expected peak of 596 *m/z* $(M+H)^+$, many unidentifiable (fragmentation) signals were also visible and therefore no full proof could be withdrawn from these results. Unfortunately, due to the complexity of the spectra and the fact that no crystalline material could be obtained, full elucidation of the regio- and/or stereochemistry appeared impossible. Other ways to obtain more structural information on these compounds, such as removal of the carbamate moiety or radical deiodination, failed in all cases.

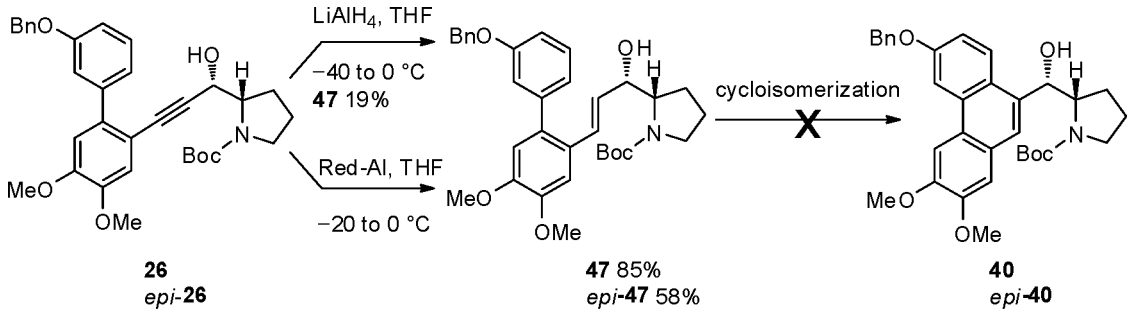
Scheme 4.14 *ICl-mediated electrophilic cyclization of* ***41****.*



41 **45** **46**

In the search for more success, we investigated the *E*-selective reduction of acetylene **26** using $LiAlH_4$. This partial reduction, however, did not proceed efficiently and the reduced product **47** was isolated in a low yield of 19% (Scheme 4.15). The in our hands most rewarding result for preparation of **47** involved exposure of acetylene **26** to Red-Al. These conditions afforded the vinylic alcohol **47** in one step and a high yield of 85%. Notably, with the same treatment, partial reduction of *epi*-**26** proceeded less smoothly to furnish *epi*-**47** in a modest yield of 58%.

Scheme 4.15 *Synthesis of vinylic alcohols* ***47****.*



26
epi-**26**

47 85%
epi-**47** 58%

40
epi-**40**

From all the possible cyclization conditions, we first opted for a photochemical ring closure. To our disappointment, irradiation of the vinylic alcohol **47** with ultraviolet light (300 nm) in acetonitrile at rt completely destroyed the starting material and led to the formation of multiple products. Alternatively, we investigated various other cycloisomerization conditions to obtain **40** and *epi*-**40**, but they unfortunately did not provide any of the desired product.

4.10 Conclusions

We aimed to develop a concise, convergent, and diastereoselective route for the synthesis of alkaloid **5** and its isomers, with which both the relative and absolute stereochemistry could be predictably installed. In the first two synthesis routes, we investigated the preparation of a key phenanthrene cyanohydrin starting from two different acetylenic aldehydes. Synthesis of the cyanohydrin precursors proceeded without difficulties, however, we were not able to form the desired product from the asymmetric HNL-mediated hydrogen cyanide additions.

The third route describes the synthesis starting from diastereocontrolled trimethylsilyl-acetylide addition onto Boc-(*S*)-prolinal. To our delight, depending on the nature of the catalyst, we were successful in obtaining both diastereoisomers in a selective manner. This

result in principle would enable us to access all four diastereoisomers depending on the stereochemistry of the Boc-protected prolinal and of the type of catalyst. Unfortunately, numerous attempts to cycloisomerize biphenylic intermediates in a later stadium of the synthesis remained unsuccessful and prevented us from completing the total synthesis.

4.11 Acknowledgements

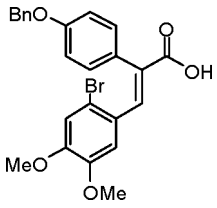
Jan M. M. Smits is gratefully acknowledged for the crystal structure determination of compound **38**. Ad E. M. Swolfs is acknowledged for assistance with the 2D NMR experiments. DSM Pharma Chemicals (Geleen, the Netherlands) is kindly acknowledged for providing the HNL enzymes.

4.12 Experimental section

General information

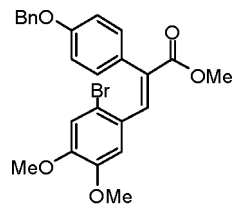
For general experimental details, see section 2.8.

(*E*)-2-[4-(Benzyloxy)phenyl]-3-(2-bromo-4,5-dimethoxyphenyl)acrylic acid (14)



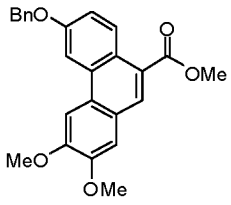
To a solution of 4-benzyloxyphenylacetic acid **15** (950 mg, 3.92 mmol) in dry THF (4 mL) was added KO^{t}Bu (449 mg, 1.02 equiv), and the mixture was stirred at rt for 2 h. After evaporation of the solvent, 2-bromo-4,5-dimethoxybenzaldehyde **16** (961 mg, 1.0 equiv) and freshly distilled Ac_2O (5 mL) were added to the residue. After heating the reaction mixture at 105 °C for 16 h, hot H_2O (10 mL) was added and stirring was continued at rt for 3h. The precipitate was filtered off and the filtrate was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and washed successively with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and concentrated *in vacuo*. The residue and the above precipitate were combined giving the crude product as a mixture of geometric isomers (*E*:*Z* = 9:1). Recrystallization from EtOH/hexane afforded **14** (1.12 g, 61% yield) as white crystals and as single isomer. R_f 0.34 (EtOAc/heptane, 1:1). Mp 196.0 °C. IR (ATR) 3002, 2941, 2842, 2595, 2509, 2263, 1679, 1596, 1500, 1261, 1213, 1163, 733, 612 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 1H), 7.42-7.30 (m, 5H), 7.18-7.14 (m, 2H), 7.01 (s, 1H), 6.98-6.94 (m, 2H), 6.36 (s, 1H), 5.06 (s, 2H), 3.85 (s, 3H), 3.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 158.7, 150.3, 147.5, 140.7, 136.9, 131.6, 131.3, 128.8, 128.2, 127.6, 127.5, 126.8, 117.6, 115.3, 115.2, 113.6, 70.1, 56.3, 55.3. HRMS (EI) *m/z* calcd for $C_{24}H_{21}BrO_5$ $(M)^+$: 468.0572, found: 468.0560.

(*E*)-2-[4-(Benzyloxy)phenyl]-3-(2-bromo-4,5-dimethoxyphenyl)acrylic acid methyl ester (17)



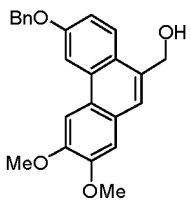
To a suspension of acrylic acid **14** (400 mg, 0.85 mmol) in dry MeCN (3 mL) were added DBU (204 µL, 1.6 equiv), and MeI (265 µL, 5.0 equiv) at rt and the mixture was stirred at the same temperature for 2.5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (3 mL), and extracted with Et_2O (3 × 10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:2) to afford **17** (357 mg, 87% yield) as a colorless oil. R_f 0.55 (EtOAc/heptane, 1:1). IR (ATR) 2954, 2842, 2254, 1708, 1597, 1500, 1265, 1239, 1210, 1172, 1026, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (s, 1H), 7.39-7.26 (m, 5H), 7.14-7.10(m, 2H), 6.97 (s, 1H), 6.95-6.91 (m, 2H), 6.30 (s, 1H), 5.02 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.0, 158.3, 149.7, 147.3, 138.5, 136.7, 132.0, 131.4, 128.5, 127.9, 127.8, 127.2, 126.8, 116.9, 114.9, 113.4, 69.8, 55.9, 55.1, 52.3. HRMS (ESI) *m/z* calcd for $C_{25}H_{24}BrO_5$ $(M+H)^+$: 483.0807, found: 483.0804.

[3-(Benzyloxy)-6,7-dimethoxyphenanthrene-9-yl]acrylic acid methyl ester (18)



To a boiling solution of acrylic methyl ester **17** (550 mg, 1.14 mmol) in dry degassed toluene (10 mL) was dropwise added a solution of Bu_3SnH (460 µL, 1.5 equiv) and ACN (167 mg, 0.6 equiv) in dry degassed toluene (6 mL) over a period of 1 h. The resulting solution was refluxed for another 3 h before it was quenched with saturated aqueous NH_4Cl (20 mL). The product was extracted from the aqueous layer with EtOAc (3 × 20 mL) and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:4) to afford **18** (362 mg, 79% yield) as a colorless oil. R_f 0.52 (EtOAc/heptane, 1:1). Mp 147.7 °C. IR (ATR) 3006, 2954, 2928, 2859, 2362, 2250, 1708, 1615, 1510, 1566, 1236, 1201, 1120, 1025, 909, 842, 733, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.94 (d, J = 9.3 Hz, 1H), 8.31 (s, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.78 (s, 1H), 7.55-7.53 (m, 2H), 7.44-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.25 (s, 1H), 5.29 (s, 1H), 4.10 (s, 3H), 4.03 (s, 3H), 4.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.3, 157.4, 151.1, 149.9, 137.1, 131.8, 129.8, 128.9, 128.5, 128.3, 127.7, 126.9, 125.7, 123.9, 123.5, 116.4, 109.4, 106.2, 103.3, 70.6, 56.2, 56.1, 52.2. HRMS (EI) *m/z* calcd for $C_{25}H_{22}O_4$ $(M)^+$: 402.1467, found: 402.1473.

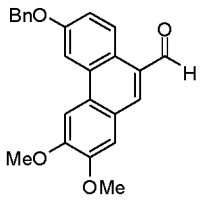
[3-(Benzyloxy)-6,7-dimethoxyphenanthren-9-yl]methanol (19)



To a suspension of $LiAlH_4$ (30 mg, 1.8 equiv) in dry THF (4 mL) at rt was added a solution of ester **18** (166 mg, 0.41 mmol) in dry THF (5 mL). The reaction mixture was heated at reflux temperature for 1 h and then cooled to rt. After dilution with Et_2O (30 mL), the mixture was carefully quenched with 1.0 M aqueous NaOH solution. After stirring for 20 min, the layers were separated and the organic layer was washed with H_2O (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by recrystallisation from benzene to afford **19** (147 mg, 95% yield) as white crystals. R_f 0.27 (EtOAc/heptane, 1:1). Mp 178.5 °C. IR (ATR) 3455, 3006, 2915, 2889, 2833, 1610, 1449, 1431, 1256, 1236, 1200, 1154, 1069, 1018, 882, 827, 735 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.76 (s, 1H), 7.55-7.52 (m, 3H), 7.44-7.40 (m, 2H), 7.37-7.29 (m, 2H), 7.16 (s, 1H), 5.28 (s, 2H), 5.11 (s, 2H), 4.07 (s, 3H), 4.00 (s, 3H), 1.82 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 149.7, 149.4, 137.2, 132.9, 131.8, 128.9, 128.3, 127.7, 127.1, 126.2,

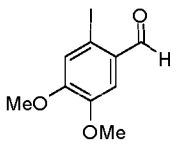
124.6, 124.4, 123.4, 115.8, 108.5, 106.5, 103.5, 70.6, 64.4, 56.2, 56.1. HRMS (EI) *m/z* calcd for $C_{24}H_{22}O_4$ $(M)^+$: 374.1518, found: 374.1511.

[3-(Benzyloxy)-6,7-dimethoxyphenanthrene-9-yl]carbaldehyde (20)



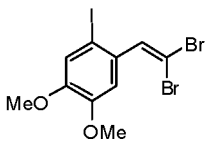
To a solution of DMSO (57 µL, 3.0 equiv) in dry CH_2Cl_2 (3 mL) was added oxalyl chloride (46 µL, 2.0 equiv) at –60 °C. To this stirred solution was slowly added alcohol **19** (100 mg, 0.27 mmol). After 15 min Et_3N (0.20 mL, 5.5 equiv) was added and the cold bath was removed after which stirring was continued for 30 min. The reaction mixture was quenched with H_2O (5 mL) and the product was extracted from the aqueous layer with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:2) to afford **20** (98 mg, 97% yield) as a white solid. R_f 0.43 (EtOAc/heptane, 1:1). Mp 198.5 °C. IR (ATR) 3023, 2924, 2816, 2362, 2332, 1675, 1611, 1594, 1253, 1203, 1157, 1046, 854, 752, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 10.24 (s, 1H), 9.32 (d, J = 9.2 Hz, 1H), 7.98 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.74 (s, 1H), 7.55-7.53 (m, 2H), 7.45-7.41 (m, 2H),7. 39-7.33 (m, 2H), 7.29 (s, 1H), 5.28 (s, 2H), 4.11 (s, 3H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.6, 157.9, 152.1, 149.9, 138.6, 137.0, 131.8, 129.0, 128.9, 128.3, 127.9, 127.7, 125.7, 122.5, 116.8, 109.6, 106.3, 103.5, 70.6, 56.3, 56.2. HRMS (EI) *m/z* calcd for $C_{24}H_{20}O_4$ $(M)^+$: 372.1362, found: 372.1363.

2-Iodo-4,5-dimethoxybenzaldehyde (29)



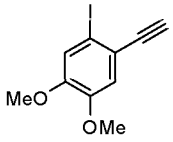
To a flask charged with dry silver trifluoroacetate (4.00 g, 1.1 equiv) was added a solution of veratrylaldehyde **28** (2.74 g, 16.5 mmol) in dry CH_2Cl_2 (120 mL) at rt. To this stirred suspension a solution of iodine (4.60 g, 1.1 equiv) in dry CH_2Cl_2 (250 mL) was added over a period of 2 h. The solution was refluxed for 12 h, at which point the reaction mixture was filtrated, washed with saturated aqueous $Na_2S_2O_3$ (200 mL), and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:7) to afford **29** (3.36 g, 70% yield) as a yellowish solid. R_f 0.39 (EtOAc/heptane, 1:2). IR (ATR) 9.87 (s, 1H), 7.42 (s, 1H), 7.31 (s, 1H), 3.96 (s, 3H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.9, 154.5, 149.8, 121.8, 111.1, 92.8, 56.6, 56.1. Data are in agreement with literature.[36]

1-(2,2-Dibromovinyl)-2-iodo-4,5-dimethoxybenzene (30)



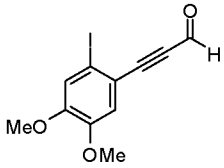
To a solution of PPh_3 (2.24 g, 5.0 equiv) in dry CH_2Cl_2 (26 mL) was added CBr_4 (1.42 g, 2.5 equiv) and the resulting yellow mixture is stirred for 10 min at 0 °C. A solution of aldehyde **29** (500 mg, 1.71 mmol) in dry CH_2Cl_2 (17 mL) is slowly introduced and stirring is continued for 1 h at that temperature. The reaction mixture was quenched with brine (50 mL), and the product was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:4) to afford **30** (705 mg, 92% yield) as a white solid. R_f 0.52 (EtOAc/heptane, 1:2). Mp 92.0 °C. IR (ATR) 3002, 2954, 2933, 2907, 2842, 1589, 1496, 1436, 1375, 1257, 1207, 1162, 1026, 868, 826. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36 (s, 1H), 7.25 (s, 1H), 7.11 (s, 1H), 3.87 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.6, 149.0, 140.6, 132.1, 121.2, 112.7, 92.2, 87.5, 56.3, 56.2. HRMS (EI) *m/z* calcd for $C_{10}H_9IBr_2O_2$ $(M)^+$: 445.8015, found: 445.8012.

1-Ethynyl-2-iodo-4,5-dimethoxybenzene (31)



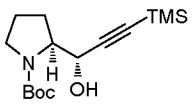
To a solution of dibromide **30** (6.00 g, 13.4 mmol) in dry THF (250 mL) at –78 °C was added LDA (27.0 mL of a 2.0 M solution in THF, 53.6 mmol, 4.0 equiv) and stirring is continued at that temperature for 5h. The reaction mixture was quenched with saturated aqueous NH_4Cl (250 mL), and the product was extracted from the aqueous layer with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:9) to afford **31** (3.17 g, 82% yield) as a white solid. R_f 0.47 (EtOAc/heptane, 1:2). Mp 106.8 °C. IR (ATR) 3287, 2967, 2933, 2842, 1588, 1500, 1252, 1211, 1159, 1026, 855, 785, 612 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (s, 1H), 6.99 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.31 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.2, 149.0, 121.1, 121.0, 115.6, 89.8, 85.5, 79.4, 56.3, 56.1. HRMS (EI) *m/z* calcd for $C_{10}H_9IO_2$ $(M)^+$: 287.9648, found: 287.9651.

3-(2-Iodo-4,5-dimethoxyphenyl)propynal (27)



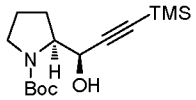
To a solution of alkyne **31** (1.65 g, 5.73 mmol) in dry THF (15 mL) at –40 °C was slowly added LDA (3.15 mL of a 2.0 M solution in THF, 6.30 mmol, 1.1 equiv) maintaining the temperature between –35 °C and –40 °C. After completion of the addition, anhydrous DMF (887 µL, 2.0 equiv) was added in one portion and the cold bath was removed. The reaction mixture was stirred for another 2 h at ambient temperature after which it was poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (30 mL, 22.9 mmol) and MTBE (30 mL) at 0 °C. After separation of the layers, the organic layer was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:6) to afford **27** (996 mg, 55% yield) as a yellowish solid. R_f 0.42 (EtOAc/heptane, 1:2). Mp 148.1 °C. IR (ATR) 3079, 3002, 2928, 2846, 2738, 2178, 1649, 1503, 1229, 1207, 1010, 902, 612. cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.47 (s, 1H), 7.28 (s, 1H), 7.06 (s, 1H), 3.92 (s, 3H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.6, 152.2, 149.2, 121.5, 118.2, 116.6, 97.4, 92.5, 90.4, 56.5, 56.2. HRMS (EI) *m/z* calcd for $C_{11}H_9IO_3$ $(M)^+$: 315.9597, found: 315.9600.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-[(*S*)-1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl]pyrrolidine (33)



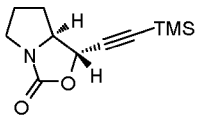
To a stirred solution of (+)-*N*-methylephedrine (880 mg, 0.4 equiv), HMPA (4.30 mL, 2.0 equiv), and trimethylsilylacetylene (6.85 mL, 4.0 equiv) in dry CH_2Cl_2 (155 mL) at rt is slowly added Et_2Zn (49.0 mL of a 1.0 M solution in hexane, 48.8 mmol, 4.0 equiv). After the solution is stirred at rt for 16 h, Boc-(*S*)-prolinal **35** (2.43 g, 12.2 mmol) is added in one portion and the reaction is allowed to proceed at rt for 4 h. The reaction mixture was slowly quenched with a 1.0 M solution of tartaric acid (100 mL), and the product was extracted with CH_2Cl_2 (3 × 80 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:4) to afford **33** (3.31 g, 71% yield) as a colorless oil. R_f 0.74 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –79.6 (*c* 1.02, CH_2Cl_2). IR (ATR) 3382, 2975, 2880, 2172, 1695, 1670, 1400, 1366, 1249, 1165, 1120, 1052, 843, 760 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.06 (bs, 1H), 4.32 (d, J = 5.2 Hz, 1H), 4.01-3.98 (m, 1H), 3.43-3.29 (m, 2H), 2.08-1.74 (m, 4H), 1.45 (s, 9H), 0.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.7, 105.3, 89.9, 80.8, 67.7, 62.9, 47.8, 28.9, 28.6, –0.1. HRMS (ESI) *m/z* calcd for $C_{15}H_{28}NO_3Si$ $(M+H)^+$: 298.1838, found: 298.1837.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl]pyrrolidine (*epi*-33)



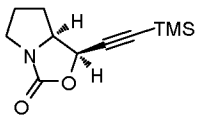
To a stirred solution of (*S*)-BINOL (1.44 g, 0.4 equiv), HMPA (4.37 mL, 2.0 equiv), and trimethylsilylacetylene (7.04 mL, 4.0 equiv) in dry CH_2Cl_2 (160 mL) at rt is slowly added Et_2Zn (50.2 mL of a 1.0 M solution in hexane, 50.2 mmol, 4.0 equiv). After the solution is stirred at rt for 16 h, $Ti(O^iPr)_4$ (3.73 mL, 1.0 equiv) and stirring is continued for 1h. Next, Boc-(*S*)-prolinal **35** (2.50 g, 12.5 mmol) is added in one portion and the reaction is allowed to proceed at rt for 4 h. The reaction mixture was slowly quenched with a 1.0 M solution of tartaric acid (100 mL), and the product was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:4) to afford *epi*-**33** (2.95 g, 72% yield) as a colorless oil. R_f 0.72 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –126.8 (*c* 1.01, CH_2Cl_2). IR (ATR): 3391, 2967, 2876, 2168, 1692, 1668, 1397, 1249, 1163, 1126, 1048, 841, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.14 (d, *J* = 9.2 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.05 (m, 1H), 3.57-3.51 (m, 1H), 3.34-3.28 (m, 1H), 2.16-2.07 (m, 1H), 2.04-1.95 (m, 1H), 1.82-1.69 (m, 2H), 1.49 (s, 9H), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.3, 104.5, 89.7, 80.6, 67.9, 63.5, 48.5, 29.5, 28.6, 24.0, 0.0. HRMS (ESI) *m/z* calcd for $C_{15}H_{28}NO_3Si$ $(M+H)^+$: 298.1838, found: 298.1833.

(1*S*,7*S*)-Tetrahydro-1-[2-(trimethylsilyl)ethynyl]-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (36)



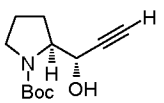
To a flask charged with TMS-acetylene **33** (57 mg, 0.19 mmol) was added a 2 M solution HCl/EtOAc (3 mL) which was stirred at rt for 2 h. After concentration *in vacuo*, the crude product was dissolved in dry THF (3 mL) and Et_3N (46 µL, 1.5 equiv) and $(Im)_2CO$ (72 mg, 2.0 equiv) were added successively at rt. The resulting reaction mixture was heated to 50 °C and stirred overnight. After cooling to rt the mixture was concentrated *in vacuo*. Column chromatography (EtOAc/heptane, 0:1→1:3) afforded the desired product **36** (30 mg, 70%) as a colorless oil. R_f 0.59 (EtOAc/heptane, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.86 (d, *J* = 4.0 Hz, 1H), 3.88 (ddd, *J* = 4.0, 7.0, 9.7 Hz, 1H), 3.61 (ddd, *J* = 7.5, 11.3 Hz, 1H), 3.16 (ddd, *J* = 4.5, 9.0, 11.3 Hz, 1H), 2.15-1.99 (m, 2H), 196-186 (m, 1H), 1.46 (ddd, *J* = 8.9, 12.0, 17.7 Hz, 1H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.7, 100.7, 93.6, 69.5, 66.2, 46.0, 30.5, 25.6, –0.3. HRMS (ESI) *m/z* calcd for $C_{11}H_{18}NO_2Si$ $(M+H)^+$: 224.1107, found: 224.1106.

(1*R*,7*S*)-Tetrahydro-1-[2-(trimethylsilyl)ethynyl]-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (*epi*-36)



Prepared as described above starting from TMS-acetylene *epi*-**33** (50 mg, 0.17 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:3) afforded *epi*-**36** (25 mg, 66% yield) as a colorless oil. R_f 0.53 (EtOAc/heptane, 1:1). IR (ATR): 2958, 2898, 2353, 2340, 2172, 1756, 1372, 1247, 1217, 1039, 843, 762 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.28 (d, *J* = 8.0 Hz, 1H), 4.02-3.96 (m, 1H), 3.72-3.65 (m, 1H), 3.20-3.13 (m, 1H), 2.10-2.01 (m, 1H), 1.97-1.85 (m, 3H), 0.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.2, 97.6, 95.9, 67.5, 62.1, 46.7, 27.9, 25.4, –0.3. HRMS (ESI) *m/z* calcd for $C_{11}H_{18}NO_2Si$ $(M+H)^+$: 224.1107, found: 224.1096.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-[(*S*)-1-hydroxyprop-2-ynyl]pyrrolidine (38)



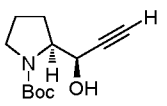
To a solution of TMS-acetylene **33** (2.39 g, 8.03 mmol) in MeOH (80 mL) at 0 °C was added K_2CO_3 (1.34 g, 1.2 equiv). The solution was stirred for 1.5 h at rt after which the reaction mixture was quenched with saturated aqueous NH_4Cl (80 mL) and CH_2Cl_2 (100 mL) was added. The product was extracted with CH_2Cl_2 (3 × 80 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by

column chromatography (EtOAc/heptane, 0:1→1:1) to afford **38** (1.77 g, 98% yield) as a white solid. R_f 0.42 (EtOAc/heptane, 1:1). Mp 65.4 °C. $[\alpha]_D^{20}$ –90.0 (*c* 0.30, CH_2Cl_2). IR (ATR) 3386, 3296, 2971, 2928, 2881, 1667, 1401, 1367, 1163, 1121, 1053, 655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.26 (bs, 1H), 4.33-4.31 (m, 1H), 4.09-4.01 (m, 1H), 3.47-3.42 (m, 1H), 3.35 (ddd, *J* = 5.1, 7.3, 10.8 Hz, 1H), 2.43 (d, *J* = 2.2 Hz, 1H), 2.13-1.77 (m, 4H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.8, 83.5, 80.9, 73.2, 67.3, 62.7, 47.8, 28.8, 28.7, 23.9. HRMS (ESI) *m/z* calcd for $C_{12}H_{20}NO_3$ $(M+H)^+$: 226.1443, found: 226.1445.

*Crystal data and structure refinement for compound **38**.*

Crystal color	translucent colourless
Crystal shape	rough fragment
Crystal size	0.28 × 0.23 × 0.10 mm
Emperical formula	$C_{12}H_{19}NO_3$
Molecular mass	225.28
Temperature	208(2) K
Radiation / wavelength	MoKα (graphite mon.) / 0.71073 Å
Crystal system, space group	Monoclinic, *P* 2_1
Unit cell dimensions	a = 10.3970(5) Å, α = 90.00°
	b = 9.0783(4) Å, β = 100.496(4)°
	c = 13.7165(7) Å, γ = 90.00°
Volume	1273.00(11) $Å^3$
Z, calculated density	4, 1.175 mg/m^3
Absorption coefficient	0.084 mm^{-1}
Diffractometer / scan	Nonius Kappa CCD with area detector f and w scan
F(000)	488
θ range for data collection	1.51° – 27.51°
Index ranges	$-13 \leq h \geq 13$, $-11 \leq k \geq 11$, $-17 \leq l \geq 17$
Reflections collected / unique	39971 / 5852 [R(int) = 0.0331]
Reflections observed	4760 ($[I_o > 2\sigma(I_o)]$)
Absorption correction	SADABS multiscan correction (Sheldrick, 1996)
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	5852 / 1 / 309
Goodness-of-fit on F^2	1.087
SHELXL-97 weight parameters	0.0527, 0.2229
Final R índices [I>2σ(I)]	R_1 = 0.0492, wR_2 = 0.1059
R índices (all data)	R_1 = 0.0652, wR_2 = 0.1144
Absolute structure parameter	–0.2(10)
Largest diff. peak and hole	0.199 and –0.179 $e \cdot Å^{-3}$

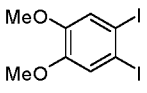
(*S*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-1-hydroxyprop-2-ynyl]pyrrolidine (*epi*-38)



Prepared as described above starting from TMS-acetylene *epi*-**33** (1.50 g, 5.04 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:1) afforded *epi*-**38** (1.10 g, 97% yield) as a white solid. R_f 0.65 (EtOAc/heptane, 1:1). Mp = 121.2. $[\alpha]_D^{20}$ –93.7 (*c* 0.84, CH_2Cl_2). IR (ATR): 3399, 3253, 2971, 2125, 16.42, 1424, 1176 cm^{-1}. ^1H NMR ($CDCl_3$,

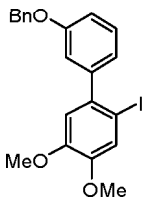
400 MHz): δ 6.16 (d, *J* = 8.8 Hz, 1H), 4.42 (d, *J* = 8.8 Hz, 1H), 4.06 (m, 1H), 3.58-3.53 (m, 1H), 3.38-3.32 (m, 1H), 2.36 (m, 1H), 2.17-2.08 (m, 1H), 2.04-1.95 (m, 1H), 1.83-1.70 (m, 2H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 82.6, 80.8, 73.2, 67.1, 63.2, 48.5, 29.3, 28.6, 24.0. HRMS (ESI) *m/z* calcd for $C_{12}H_{19}NO_3Na$ $(M+Na)^+$: 248.1263, found: 248.1257.

1,2-Diiodo-4,5-dimethoxybenzene (34)



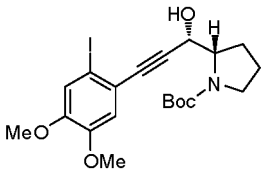
To a solution of orthoperiodic acid (8.25 g, 0.5 equiv) in EtOH (450 mL) were successively added at rt veratrole **37** (10.0 g, 72.4 mmol), and iodine (16.5 g, 0.9 equiv). After stirring for 16 h at 70 °C, the mixture was cooled to ambient temperature and saturated aqueous $Na_2S_2O_3$ (200 mL) was added by which the color of the reaction mixture changed from purple to white. White precipitates were filtered off, and the filtrate was washed with H_2O (2 × 200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:4) to afford **34** (280.1 g, 99% yield) as a white solid. R_f 0.64 (EtOAc/heptane, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (s, 2H), 3.83 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.7, 121.7, 96.2, 56.3. Data are in agreement with literature.[37]

3'-(Benzyloxy)-2-iodo-4,5-dimethoxybiphenyl (32)



To a solution of diiodide **34** (0.13 g, 0.33 mmol) in DME (2.5 mL) were successively added a solution of aqueous 2.0 M Na_2CO_3 (0.83 mL, 5.0 equiv) and LiCl (42 mg, 3.0 equiv). After degassing the solution for 20 min by bubbling a stream of argon through the solution $Pd(dppf)_2Cl_2$ (14 mg, 5.5 mol %) and 3-(benzyloxy)phenylboronic acid (82 mg, 1.08 equiv) were added in one portion. After stirring for 3 h at 70 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and the product was extracted from the aqueous layer with MTBE (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:3) to afford **32** (125 mg, 84% yield) as a colorless oil. R_f 0.48 (EtOAc/heptane, 1:3). IR (ATR) 3062, 3032, 2997, 2933, 2833, 2258, 1601, 1597, 1502, 1482, 1241, 1207, 1167, 1025, 855, 775, 733, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.44 (m, 2H), 7.39-7.36 (m, 2H), 7.34-7.29 (m, 3H), 7.00-6.92 (m, 3H), 6.81 (s, 1H), 5.10 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 149.2, 148.8, 145.5, 139.1, 137.1, 129.1, 128.7, 128.0, 127.6, 122.3, 121.8, 116.2, 114.2, 113.1, 86.1, 70.2, 56.3, 56.0. HRMS (EI) *m/z* calcd for $C_{21}H_{19}IO_3$ $(M)^+$: 446.0379, found: 446.0382.

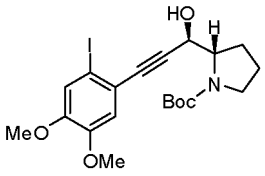
(*S*)-*N*-*tert*-Butoxycarbonyl-2-[(*S*)-1-hydroxy-3-(2-iodo-4,5-dimethoxyphenyl)prop-2-ynyl]pyrrolidine (39)



To a flask charged with $Pd(PPh_3)_2Cl_2$ (426 mg, 5 mol %) and CuI (281 mg, 20 mol %) was added a solution of diiodide **34** (6.32 g, 2.5 equiv) in degassed benzene (45 mL). Then the mixture was cooled to 0 °C and Et_2NH (5.31 mL, 7.0 equiv) and alkyne **38** (1.66 g, 7.37 mmol) were added successively. After being stirred for 4 h at rt, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the product was extracted with MTBE (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:1) to afford **39** (3.30 g, 92% yield) as a yellow solid. R_f 0.29 (EtOAc/heptane, 1:2). Mp 71.2 °C. $[\alpha]_D^{20}$ −53.1 (*c* 1.09, CH_2Cl_2). IR (ATR) 3378, 2971, 2928, 2245, 1668, 1504, 1401, 1258, 1206, 1030, 911, 732 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (s, 1H), 6.97 (s, 1H), 5.35 (bs, 1H), 4.59 (d, *J* = 6.5 Hz, 1H), 4.19 (dd, *J* = 6.5, 12.1 Hz, 1H), 3.86

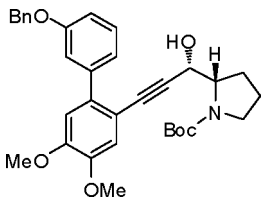
(s, 3H), 3.84 (s, 3H), 3.48-3.38 (m, 2H), 2.20-2.19 (m, 2H), 1.98-1.80 (m, 2H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.9, 149.8, 149.0, 121.7, 121.0, 115.4, 90.9, 89.8, 87.1, 80.9, 68.1, 63.0, 56.3, 56.2, 47.9, 29.4, 28.6, 24.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{27}INO_5$ $(M+H)^+$: 488.0934, found: 488.0940.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-1-hydroxy-3-(2-iodo-4,5-dimethoxyphenyl)prop-2-ynyl]pyrrolidine (*epi*-39)



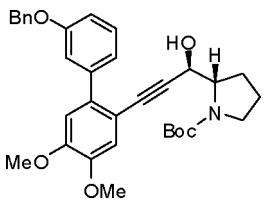
Prepared as described above starting from alkyne *epi*-**38** (1.00 g, 4.44 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:2) afforded *epi*-**39** (2.01 g, 93% yield) as a yellowish oil. R_f 0.33 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ −110.6 (*c* 1.26, CH_2Cl_2). IR (ATR): 3343, 2967, 2932, 2872, 2837, 2254, 1664, 1503, 1405, 1167, 730 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (s, 1H), 6.95 (s, 1H), 6.32 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 4.15 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.60-3.49 (m, 2H), 2.23-2.14 (m, 1H), 2.08-1.94 (m, 2H), 1.81-1.72 (m, 1H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 149.8, 149.0, 122.0, 121.0, 115.5, 90.0, 89.2, 87.1, 80.7, 67.8, 63.4, 56.3, 56.1, 48.7, 29.5, 28.7, 24.2. HRMS (ESI) *m/z* calcd for $C_{20}H_{27}INO_5$ $(M+H)^+$: 488.0934, found: 488.0929.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-{(*S*)-3-[3'-(benzyloxy)-4,5-dimethoxybiphenyl-2-yl]-1-hydroxyprop-2-ynyl}pyrrolidine (26)



To a solution of iodide **39** (1.00 g, 2.05 mmol) in DME (16 mL) was successively added a solution of aqueous 2.0 M Na_2CO_3 (5.13 mL, 5.0 equiv) and LiCl (261 mg, 3.0 equiv). After degassing the solution for 20 min by bubbling a stream of argon through the solution $Pd(dppf)_2Cl_2$ (83.0 mg, 5.5 mol %) and 3-(benzyloxy)phenylboronic acid (505 mg, 1.08 equiv) were added in one portion. After stirring for 3 h at 70 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and the product was extracted from the aqueous layer with MTBE (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 0:1→1:2) to afford **26** (891 mg, 81% yield) as a yellow solid. R_f 0.54 (EtOAc/heptane, 1:1). Mp 56.8 °C. $[\alpha]_D^{20}$ −49.1 (*c* 1.01, CH_2Cl_2). IR (ATR) 3378, 3343, 2971, 2933, 2881, 2842, 2250, 1671, 1514, 1394, 1251, 1153, 1031, 909, 730, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.44 (m, 2H), 7.40-7.36 (m, 2H), 7.33-7.29 (m, 2H), 7.19 (s, 1H), 7.15-7.13 (m, 1H), 7.07 (s, 1H), 6.96-6.93 (m, 1H), 6.81 (s, 1H), 5.33 (d, *J* = 2.7 Hz, 1H), 5.11 (s, 2H), 4.41 (dd, *J* = 2.7, 5.4 Hz, 1H), 3.96-3.93 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.36-3.30 (m, 1H), 3.26-3.20 (m, 1H), 1.75-1.59 (m, 4H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 157.7, 149.3, 147.9, 142.0, 137.4, 137.1, 129.0, 128.6, 128.0, 127.6, 122.0, 116.0, 115.5, 113.6, 113.0, 112.3, 90.0, 84.7, 80.7, 70.1, 67.9, 62.9, 56.1, 56.0, 47.7, 28.6, 28.5, 23.8. HRMS (ESI) *m/z* calcd for $C_{33}H_{38}NO_6$ $(M+H)^+$: 544.2699, found: 544.2724.

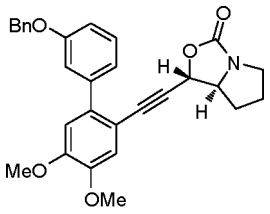
(*S*)-*N*-*tert*-Butoxycarbonyl-2-{(*R*)-3-[3'-(benzyloxy)-4,5-dimethoxybiphenyl-2-yl]-1-hydroxyprop-2-ynyl}pyrrolidine (*epi*-26)



Prepared as described above starting from iodide *epi*-**39** (1.50 g, 3.08 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:2) afforded *epi*-**26** (1.41 g, 84% yield) as a yellowish solid. R_f 0.26 (EtOAc/heptane, 1:2). Mp 55.7 °C. $[\alpha]_D^{20}$ −86.5 (*c* 1.41, CH_2Cl_2). IR (ATR): 3516, 3373, 3317, 2963, 2928, 2846, 2250, 2215, 1665, 1514, 1392, 1251, 1152, 1026, 732

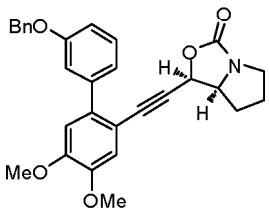
cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.28 (m, 6H), 7.16-7.12 (m, 2H), 7.04 (s, 1H), 6.96-6.93 (m, 1H), 6.80 (s, 1H), 6.02 (d, *J* = 8.5 Hz), 5.10 (s, 2H), 4.56 (d, *J* = 8.5 Hz), 3.99 (dd, *J* = 6.9, 6.9 Hz), 3.89 (s, 3H), 3.88 (s, 3H), 3.35-3.32 (m, 1H), 2.88-2.82 (m, 1H), 1.94-1.88 (m, 1H), 1.61-1.44 (m, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 157.2, 149.2, 148.0, 142.2, 137.1, 129.1, 128.7, 128.1, 127.7, 127.6, 122.1, 116.0, 115.7, 113.6, 113.3, 112.4, 89.0, 84.8, 80.5, 70.2, 67.6, 63.3, 56.2, 56.1, 48.2, 29.0, 28.5, 23.9. HRMS (ESI) *m/z* calcd for $C_{33}H_{38}NO_6$ $(M+H)^+$: 544.2699, found: 544.2702.

(1*S*,7*S*)-Tetrahydro-1-{2-[3'-(Benzyloxy)-4,5-dimethoxybiphenyl-2-yl]ethynyl}-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (41)



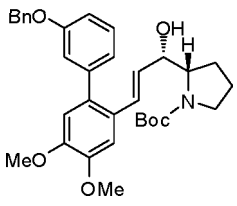
To a stirred solution of biphenyl **26** (150 mg, 0.276 mmol) and 2,6-lutidine (140 µL, 4.3 equiv) in dry CH_2Cl_2 (3 mL) at 0 °C was added dropwise TMSOTf (200 µL, 4.0 equiv). The reaction mixture was stirred for 3 h at rt, quenched with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in dry THF (3 mL) and freshly distilled Et_3N (115 µL, 3.0 equiv) and $(Im)_2CO$ (160 mg, 3.5 equiv) were added successively at rt. The resulting reaction mixture was heated to 50 °C and stirred overnight. After cooling to rt the mixture was concentrated *in vacuo*. Column chromatography (EtOAc/heptane, 0:1→1:1) afforded the desired product **41** (1.02 g, 79%) as an off-white solid. R_f 0.31 (EtOAc/heptane, 1:1). Mp 49.3 °C. $[\alpha]_D^{20}$ –67.6 (*c* 0.63, CH_2Cl_2). IR (ATR) 2963, 2928, 2898, 2837, 2228, 1754, 1515, 1251, 1207, 1155, 1025, 780, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48-7.45 (m, 2H), 7.41-7.36 (m, 2H), 7.35-7.30 (m, 2H), 7.21-7.20 (m, 1H), 7.16-7.14 (m, 1H), 7.04 (s, 1H), 6.99-6.96 (m, 1H), 6.85 (s, 1H), 5.10 (s, 2H), 4.98 (d, *J* = 4.0 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.78 (ddd, *J* = 4.0, 6.0, 9.7 Hz, 1H), 3.63-3.56 (m, 1H), 3.09 (ddd, *J* = 4.6, 9.1, 11.4 Hz, 1H), 2.05-1.94 (m, 2H), 1.85-1.75 (m, 1H), 1.47-1.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.3, 158.5, 150.1, 148.0, 141.5, 138.1, 137.1, 129.1, 128.6, 128.0, 127. 5, 121.9, 115.9, 115.5, 113.8, 112.4, 111.5, 87.8, 86.0, 70.1, 69.9, 65.9, 56.2, 56.1, 45.8, 30.2, 25.5. HRMS (ESI) *m/z* calcd for $C_{29}H_{29}NO_5$ $(M+H)^+$: 470.1968, found: 470.1963.

(1*R*,7*S*)-Tetrahydro-1-{2-[3'-(benzyloxy)-4,5-dimethoxybiphenyl-2-yl]ethynyl}-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (*epi*-41)



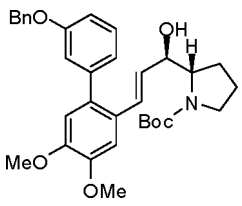
Prepared as described above starting from biphenyl *epi*-**26** (1.20 g, 2.21 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:2) afforded *epi*-**41** (798 mg, 77% yield) as a off-white solid. R_f 0.32 (EtOAc/heptane, 1:1). Mp 58.7 °C. $[\alpha]_D^{20}$ –17.5 (*c* 1.05, CH_2Cl_2). IR (ATR) 2971, 2928, 2898, 2842, 2232, 1753, 1601, 1515, 1376, 1254, 1221, 1162, 1026, 776, 733, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.45 (m, 2H), 7.41-7.37 (m, 2H), 7.35-7.30 (m, 2H), 7.12-7.08 (m, 2H), 7.03 (s, 1H), 6.99-6.96 (m, 1H), 6.82 (s, 1H), 5.39 (d, *J* = 7.9 Hz, 1H), 5.10 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90-3.87 (m, 1H), 3.59 (ddd, *J* = 6.9, 8.1, 11.3 Hz, 1H), 3.09 (ddd, *J* = 4.3, 8.8, 11.3 Hz, 1H), 1.88-1.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.2, 158.7, 150.1, 148.1, 141.8, 138.4, 137.1, 129.3, 128.7, 128.1, 127.7, 122.1, 116.1, 115.6, 113.8, 112.5, 111.7, 89.6, 83.1, 70.2, 68.1, 62.4, 56.3, 56.2, 46.6, 27.6, 25.5. HRMS (ESI) *m/z* calcd for $C_{29}H_{28}NO_5$ $(M+H)^+$: 470.1968, found: 470.1953.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-{(*S*,*E*)-3-[3'-(benzyloxy)-4,5-dimethoxybiphenyl-2-yl]-1-hydroxyprop-2-enyl}pyrrolidine (47)



To a solution of biphenyl **26** (1.34 g, 2.46 mmol) in dry THF (30 mL) at –20 °C was dropwise added Red-Al (903 µL of a 65 wt. % solution in toluene, 2.96 mmol, 1.2 equiv). After addition was complete, the solution was allowed to warm to 0 °C over 3 h and carefully quenched by the addition of aqueous 0.1 M HCl (2 mL). The resulting solution was diluted with EtOAc (60 mL) and H_2O (60 mL). The aqueous layer was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (EtOAc/heptane, 0:1→1:1) afforded the desired product **47** (1.14 g, 85%) as a white foam. R_f 0.29 (EtOAc/heptane, 1:2). Mp 60.3 °C. $[\alpha]_D^{20}$ –55.6 (*c* 1.07, CH_2Cl_2). IR (ATR) 3352, 2971, 2937, 2876, 2250, 1661, 1510, 1398, 1246, 1162, 1135, 910, 730, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.28 (m, 6H), 7.11 (s, 1H), 6.96-6.91 (m, 3H), 6.76 (s, 1H), 6.54 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 7.7, 15.8 Hz, 1H), 5.42 (bs, 1H), 5.08 (s, 2H), 3.99-3.94 (m, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.51-3.39 (m, 1H), 3.31-3.26 (m, 1H), 1.91-1.65 (m, 4H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 158.1, 158.0, 148.6, 142.3, 137.1, 133.8, 131.1, 129.3, 129.1, 128.7, 128.1, 127.6, 127.4, 122.9, 116.7, 113.3, 112.9, 108.9, 80.7, 78.5, 70.1, 62.9, 56.2, 56.1, 47.6, 28.9, 28.6, 24.0. HRMS (ESI) *m/z* calcd for $C_{33}H_{39}NO_6Na$ $(M+Na)^+$: 568.2675, found: 568.2680.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-{(*R*,*E*)-3-[3'-(benzyloxy)-4,5-dimethoxybiphenyl-2-yl]-1-hydroxyprop-2-enyl}pyrrolidine (*epi*-47)



Prepared as described above starting from biphenyl *epi*-**26** (245 mg, 0.451 mmol). Purification by column chromatography (EtOAc/heptane, 0:1→1:1) afforded *epi*-**47** (143 mg, 58% yield) as acolorless oil. R_f 0.24 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –79.1 (*c* 0.82, CH_2Cl_2). IR (ATR) 3382, 2971, 2928, 2353, 2332, 1684, 1511, 1396, 1248, 1167, 1136, 1028, 608 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.44 (m, 2H), 7.41-7.37 (m, 2H), 7.35-7.28 (m, 2H), 7.07 (s, 1H), 6.97-6.90 (m, 3H), 6.76 (s, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 5.94 (dd, *J* = 7.5, 15.7 Hz, 1H), 5.12 (bs, 1H), 5.09 (s, 2H), 4.17-4.10 (m, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.50-3.46 (m, 1H), 3.25-3.18 (m, 1H), 2.01-1.67 (m, 4H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.7, 148.6, 148.5, 142.3, 137.1, 133.8, 131.1, 129.2, 128.7, 128.1, 127.7, 122.9, 116.7, 113.3, 113.0, 109.2, 80.4, 76.3, 70.2, 63.3, 56.2, 56.1, 48.3, 29.8, 28.6, 24.2. HRMS (ESI) *m/z* calcd for $C_{33}H_{39}NO_6Na$ $(M+Na)^+$: 568.2675, found: 568.2660.

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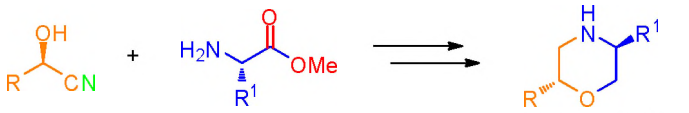
Chapter 5

Enantioselective Chemoenzymatic Synthesis of *cis*- and *trans*-2,5-Disubstituted Morpholines



All 4 possible diastereoisomers

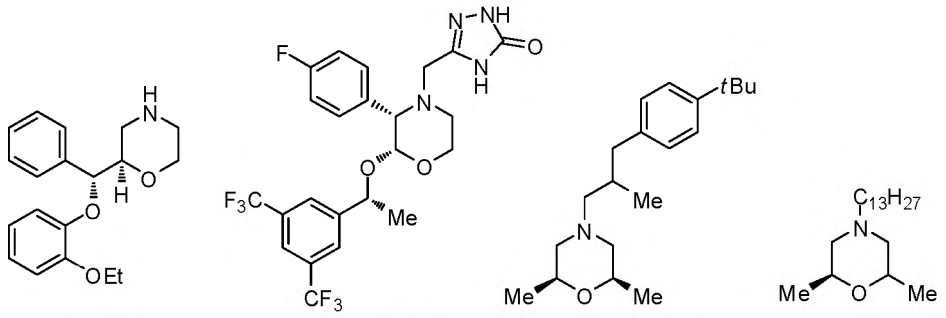
A versatile synthesis of enantiomerically pure *cis*- and *trans*-2,5-disubstituted morpholines is described. Hydroxynitrile lyase-mediated cyanide addition onto aldehydes provided cyanohydrins in virtually quantitative yield and excellent enantioselectivity. Subsequent formation of diastereomerically pure amino esters *via* a three-step one-pot reduction–transimination–reduction sequence, followed by reduction and simultaneous protection provided the cyclization precursors. Finally, cyclization and SmI_2-mediated reductive detosylation completed the synthesis of *cis*- and *trans*-2,5-disubstituted morpholines in good yields and excellent diastereoselectivities.

Part of this chapter has been published: Ritzen, B.; Hoekman, S.; Durán Verdasco, E.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2010**, *75*, 3461–3464.

5.1 Introduction

Substituted morpholines have attracted considerable interest due to their presence in a vast number of therapeutically and biologically active compounds.[1] For instance, reboxetine (**1**), a potent antidepressant drug, selectively inhibits the norepinephrine reuptake and is widely studied for its pharmacological properties (Figure 5.1).[2] Aprepitant (**2**) has recently been approved in combination with other agents as an effective treatment for preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV) resulting from highly emetogenic chemotherapy in adults.[3] The morpholine skeleton is also of importance for the construction of a large class of agrochemical fungicides and bactericides. Fenpropimorph (**3**) and tridemorph (**4**, both mixtures of isomers) for example, both ergosterol biosynthesis inhibitors, are used as agricultural fungicides in cereals.[4] Furthermore, morpholines have been applied as chiral auxiliaries in asymmetric synthesis,[5] albeit that general application is somewhat limited due to restricted access to stereoselective entries into these kinds of molecules. Despite their importance, applications in organic synthesis are most frequently restricted to simple bases or *N*-alkylating agents. Less attention has been devoted to the synthesis of *C*-funtionalized morpholine derivatives, a compound class that may have important applications in the ongoing search to new pharmaceutically active compounds. As a consequence, the development of efficient synthetic routes to *C*-funtionalized morpholines has been an important subject of investigation over the past decades. Various classes of chiral *C*-functionalized disubstituted morpholine derivatives have been synthesized.[1,5,6] To the best of our knowledge, only two enantioselective synthetic routes to *trans*-2,5-disubstituted morpholines exist,[1b,7] and only one that provides access to both *cis*- and *trans*-2,5-disubstituted morpholines.[8] However, all three strategies are rather limited in their substitution pattern or produce the target morpholines with only modest diastereoselectivity.

Figure 5.1 *Biologically active morpholines.*



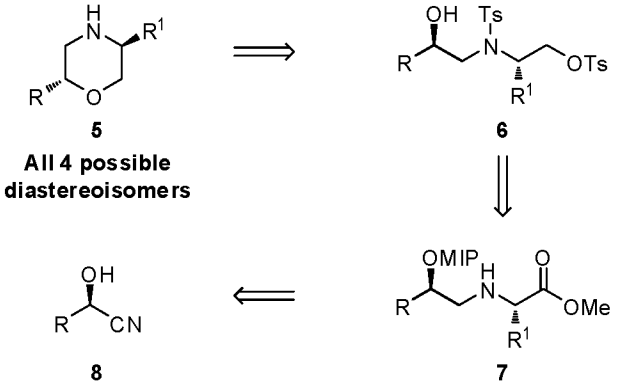
1 reboxetine **2** aprepitant **3** fenpropimorph **4** tridemorph

5.2 Retrosynthetic strategy

We recently reported a concise asymmetric synthesis of 2,3-disubstituted *trans*-aziridines starting from enantiomerically pure cyanohydrins.[9] Considering the general value of morpholines, we felt that a similar cyanohydrin-based strategy could be applied to the construction of both *cis*- and *trans*-2,5-disubstituted morpholines.

The retrosynthetic plan is outlined in Scheme 5.1. We envisioned obtaining the morpholines **5** in enantiopure form starting from cyanohydrins **8** and amino esters as building blocks, which are readily available in both enantiomeric forms. The target molecules **5** could arise *via* ring-closure of the amino diols **6**, followed by deprotection under mild reductive conditions. The intermediates **6**, in turn, might be accessed by coupling amino acid methyl esters with cyanohydrins **8** in a transimination reaction. Finally, chemoenzymatic cyanohydrin formation was envisioned to provide the starting compounds **8** with high enantioselectivity using aldehydes as substrates.

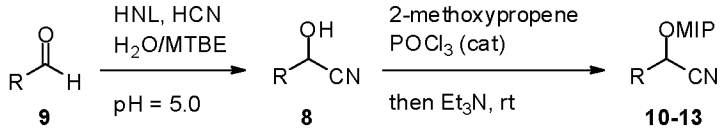
Scheme 5.1 *Retrosynthetic route to chiral morpholines.*

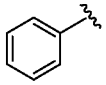
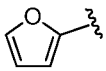
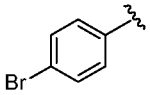
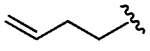


5.3 Chemoenzymatic asymmetric cyanohydrin formation

The synthesis commenced with the preparation of enantiomerically pure cyanohydrins[10] Starting from four different aldehydes and using (*R*)-selective HNL from *Prunus amygdalus* (*Pa*HNL)[11] and (*S*)-selective HNL from *Hevea brasiliensis* (*Hb*HNL)[12] as catalysts, the corresponding cyanohydrins **8** were obtained as crude products. Subsequent protection of the hydroxyl with a methoxy isopropyl (MIP) protecting group, mandatory in order to prevent racemization *via* an equilibrium with the aldehyde, afforded the cyanohydrins **10–13** (Table 5.1) in virtually quantitative yield and excellent enantiomeric excess.

Table 5.1 *HNL-mediated cyanohydrin formation and protection.*



entry	R	enzyme	product	yield (%)[a]	ee (%)	config.
1		(*R*)-HNL	**10**	99	>99[b]	(*R*)
2		(*S*)-HNL	**11**	90	>99[b]	(*R*)[d]
3		(*S*)-HNL	**12**	99	>99[b]	(*S*)
4		(*S*)-HNL	**13**	99	>99[c]	(*S*)

[a] Isolated yield after chromatography. [b] Determined by HPLC analysis of the free cyanohydrins **8**. [c] Determined by derivatization with Mosher's acid chloride and comparison with the diastereomeric

esters prepared from their racemic counterparts. [d] The stereochemical arrangement is as expected for (*S*)-HNL: however, due to priority changes following the Cahn–Ingold–Prelog rules, the product has the (*R*)-configuration.

5.4 Synthesis of MIP-protected amino alcohols

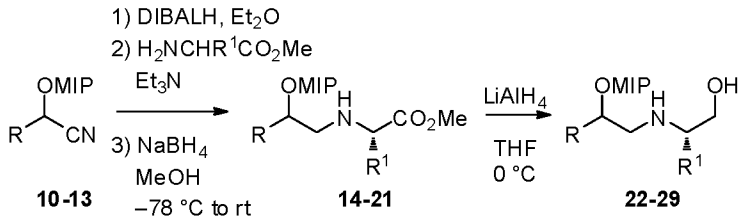
Inspired by results from van der Gen *et al.*,[13] cyanohydrin **10** was reacted in a three-step, one-pot reduction–transimination–reduction sequence to prepare the *N*-substituted β-amino ester **14**. Treatment with a 5-fold excess of DIBALH at –78 °C followed by protonation of the resulting imine–aluminum complex with dry methanol afforded the intermediate primary imine. Subsequent transimination with an excess of glycine methyl ester and Et_3N led to rapid formation of the more stable secondary imine upon loss of NH_3. Finally, the transimination product was reduced in situ with sodium borohydride at 0 °C furnishing **14** in 48% overall yield (entry 1, Table 5.2). The somewhat moderate yield for this reaction sequence can be mainly explained by overreduction of the intermediate metallo-imine to the corresponding amine with DIBALH as was shown by mass spectrometry analysis. Optimizing the conditions to keep this side reaction to a minimum proved to be difficult. Changing the addition speed or lowering the amount of DIBALH gave lower conversions, while longer exposure of the starting material under these conditions resulted in increased formation of the corresponding amine. In the course of determining the optimal conditions, we noticed that the use of the MIP protective group turned out to be critical. When the same sequence was carried out using a TBS protective group, considerable side-product formation was observed due to reductive cleavage of the TBS ether by DIBALH.[14] Furthermore, we encountered severe difficulties in deprotecting the hydroxyl group in a later stage of the synthesis. In contrast, the MIP protective group could be readily removed under mildly acidic conditions.

Pleased with these results, we applied the one-pot reaction sequence on cyanohydrins **11**–**13** using various commercially available (*S*)-amino acid methyl esters. Gratifyingly, the desired amino esters could be isolated in fair to moderate yields for the three-step sequence. In case of entry 5, only 10% yield was obtained, apparently as a result of increased reactivity of the 2-furanyl moiety toward DIBALH.

Reduction of methyl esters **14**–**21** under standard conditions ($LiAlH_4$ in THF, 0 °C) proceeded in all cases to give the corresponding amino alcohols in high yields. Alternatively, these amino alcohols might be directly obtained by coupling the cyanohydrins with the appropriate enantiopure β-amino alcohols. However, such attempts resulted in considerably

decreased product formation (10–15%) so that we decided to focus on the amino acid methyl esters.

Table 5.2 *Three-step one-pot coupling and reduction.*



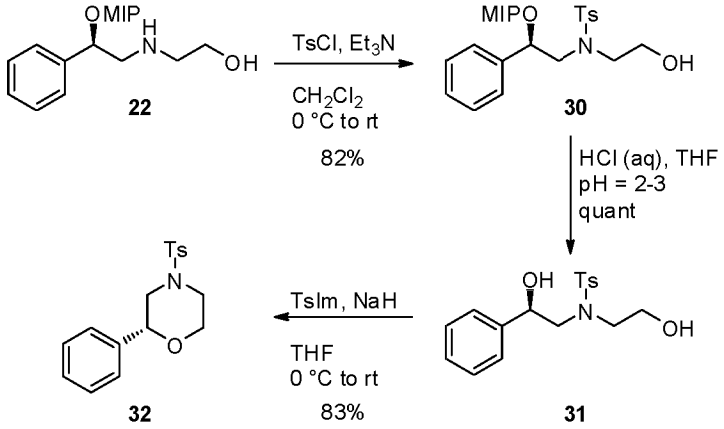
entry	s.m.	R^1	methyl ester	yield (%)[a]	amino alcohol	yield (%)[a]	config.
1	**10**	H	**14**	48	**22**	80	(*R*)
2	**10**	Me	**15**	32	**23**	92	(*R*,*S*)
3	**10**	Bn	**16**	44	**24**	89	(*R*,*S*)
4	**10**	Allyl	**17**	34	**25**	95	(*R*,*S*)
5	**11**	Bn	**18**	10	**26**	88	(*R*,*S*)
6	**12**	Me	**19**	35	**27**	87	(*S*,*S*)
7	**12**	Bn	**20**	34	**28**	92	(*S*,*S*)
8	**13**	Allyl	**21**	47	**29**	97	(*S*,*S*)

[a] Isolated yield after chromatography.

5.5 Synthesis of the morpholine scaffold

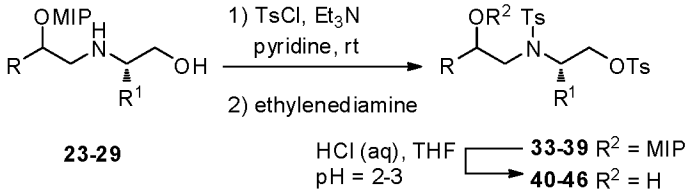
Exposure of amino alcohol **22** to an excess of *o*-nitrobenzenesulfonyl chloride (NsCl) to simultaneously react the primary alcohol and the secondary nitrogen provided the desired product in only 35% yield. In contrast, subjection of **22** to *p*-toluenesulfonyl chloride (1.1 equiv) and triethylamine (2.0 equiv) in dichloromethane at 0 °C afforded selectively the *N*-tosylated amino alcohol **30** in 82% yield (Scheme 5.2). This product was MIP-deprotected under mild acidic conditions (pH 2–3) and then cyclized in one step *via* selective tosylation of the primary alcohol involving excess sodium hydride in THF, followed by *p*-toluenesulfonyl imidazole at 0 °C. Fortunately, this provided *N*-tosylmorpholine derivative **32** in 83% yield.

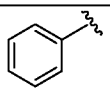
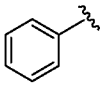
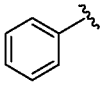
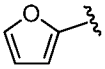
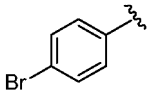
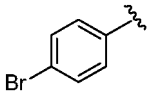
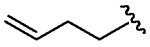
Scheme 5.2 *Synthesis of N-tosyl-protected 2-phenylmorpholine.*



Although the sequence summarized in Scheme 5.2 was highly efficient, attempts to apply the same sequence to prepare 2,5-disubstituted morpholines (R^1 = methyl, benzyl, allyl; compounds **23**–**29**, Table 5.3) only provided selective *O*-tosylation, apparently as a result of increased steric hindrance of the amino group. A more rewarding result was obtained by stirring compounds **23**–**29** in the presence of *p*-toluenesulfonyl chloride (4.0 equiv) in pyridine containing triethylamine, thereby providing **33**–**39** as summarized in Table 5.3.[1b] To facilitate purification of the products, ethylenediamine was added to scavenge the excess of *p*-toluenesulfonyl chloride. Moreover, in some cases under these circumstances cleavage of the MIP protective group took also place (entries 6 and 7). In other cases, subsequent deprotection of the hydroxyl group proceeded smoothly in high yields, and the crude morpholine precursors **40**–**46** were used without further purification for the next step.

Table 5.3 *Simultaneous sulfonylation and deprotection.*



entry	s.m.	R	R^1	product	Yield (%)[a]	product	Yield (%)[a]
1	**23**		Me	**33**	80	**40**	90
2	**24**		Bn	**34**	74	**41**	98
3	**25**		Allyl	**35**	85	**42**	95
4	**26**		Bn	**36**	70	**43**	92
5	**27**		Me	**37**	88	**44**	100
6	**28**		Bn	**38**	n.d.[b]	**45**	96[c]
7	**29**		Allyl	**39**	n.d.[b]	**46**	80[c]

[a] Isolated yield after chromatography. [b] n.d. = not determined. [c] Yield over two steps.

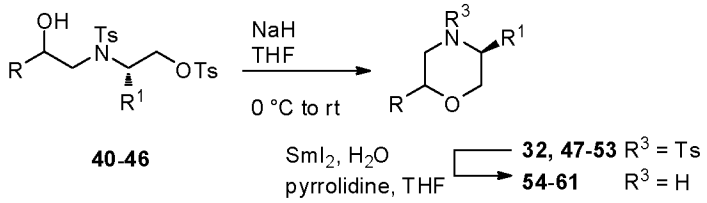
Subsequent cyclization under the influence of NaH in THF at 0 °C successfully provided the *N*-tosyl-protected morpholines **32** and **47**–**53** in high yields (Table 5.4).

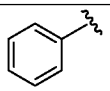
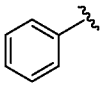
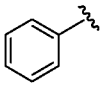
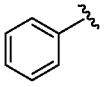
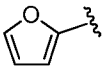
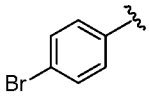
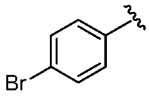
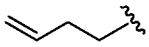
5.6 Reductive detosylation of morpholines

Finally, deprotection completed the synthesis of unprotected *cis*- and *trans*-2,5-disubstituted morpholines **54**–**61**. Generally, the robustness of sulfonamides can be problematic in the deprotection to the free amines. Traditional deprotection methods involving single electron donors such as lithium or sodium are often too harsh for these systems. Upon application of recent methodology developed by Ankner *et al.*,[15] we found that by using a combination of SmI_2/pyrrolidine/H_2O, the *N*-tosyl-protected morpholines **32** and **47**–**53** underwent clean and

instantaneous deprotection. Unfortunately, in the case of entries 6 and 7, lower yields were obtained. Mass spectrometry of the reaction mixture showed that under these reductive conditions partial dehalogenation of the aromatic ring had occurred.

Table 5.4. *Ring closure and SmI_2-mediated deprotection.*



entry	s.m.	R	R^1	product	Yield (%)[a]	product	Yield (%)[a]	Config.
1	–		H	**32**	–	**54**	80	(*R*)
2	**40**		Me	**47**	96	**55**	92	(*R*,*S*)
3	**41**		Bn	**48**	99	**56**	83	(*R*,*S*)
4	**42**		Allyl	**49**	97	**57**	86	(*R*,*S*)
5	**43**		Bn	**50**	73	**58**	82	(*S*,*S*)
6	**44**		Me	**51**	94	**59**	50	(*S*,*S*)
7	**45**		Bn	**52**	93	**60**	56	(*S*,*S*)
8	**46**		Allyl	**53**	83	**61**	86	(*S*,*S*)

[a] Isolated yield after chromatography.

5.7 Conclusions

In summary, we have described a synthetic route that effectively provides access to diastereomerically pure *cis*- and *trans*-2,5-disubstituted morpholines. Key steps involve HNL-catalyzed cyanohydrin formation, a three-step, one-pot coupling sequence, and SmI_2-mediated detosylation. Important advantages of this sequence are the ready availability of the two chiral

precursors from either simple aldehydes or commercially available amino acids and the relatively mild character of the route which, in principle, allows for introduction of various functional groups.

5.8 Acknowledgements

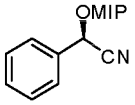
Steven Hoekman and Elena Durán Verdasco are gratefully acknowledged for their contribution to this chapter. DSM Pharma Chemicals (Geleen, the Netherlands) is kindly acknowledged for providing the HNL enzymes.

5.9 Experimental section

General information

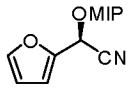
For general experimental details, see section 2.8.

(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylacetonitrile (10)



A solution of benzaldehyde (3.10 mg, 15.1 mmol) in MTBE (50 mL) was added to a cooled (0 °C) solution of KCN (9.82 g, 151 mmol, 10.0 equiv) in citrate buffer (50 mL, pH = 5.0). After addition of (*R*)-HNL (2.56 mL) the reaction mixture was stirred at 0 °C for 1.5 h and quenched with 5 M HCl (15 mL), causing the enzyme to precipitate. The precipitate was filtered off. The filtrate was extracted with CH_2Cl_2 (3 × 150 mL) and the organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 2-methoxypropene (5.78 mL, 4.0 equiv) and $POCl_3$ (3.0 µL, 0.2 mol %) was added at rt. The reaction mixture was stirred at rt for 15 min. Subsequently Et_3N (21.0 µL, 1.0 mol %) was added. The reaction mixture was stirred at rt for 10 min. After diluting the reaction mixture with Et_2O (20 mL), the organic layer was washed with brine (2 × 30 mL). The resulting organic fraction was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **10** (3.02 g, 99% yield) as a colorless oil. R_f 0.57 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +45.9 (*c* 1.03, CH_2Cl_2). {ref.[16] $[\alpha]_D^{20}$ +47.0 (*c* 1.00, $CHCl_3$)}. ee >99% (HPLC eluent hexane: *i*PrOH = 80:20, flow 1.0 mL/min); $R_{t,1}$ = 4.65 min (*S*), $R_{t,2}$ = 4.97 min (*R*). IR (ATR) 3413, 2984, 1017, 693 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51-7.35 (m, 5H), 5.46 (s, 1H), 3.20 (s, 3H), 1.55 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.0, 129.1, 128.8, 126.8, 119.1, 102.6, 61.1, 49.6, 24.7, 24.1. HRMS (FAB) *m/z* calcd for $C_{12}H_{16}NO_2$ $(M+H)^+$: 206.1181, found: 206.1185. Data are in agreement with literature.[3]

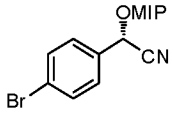
(*S*)-2-(2-Furyl)-2-[(2-methoxypropan-2-yl)oxy]acetonitrile (11)



Prepared as described above starting from furfural (1.10 g, 11.45 mmol) and (*S*)-HNL. The organic layer was washed and afforded cyanohydrin **11** (2.01 g, 90% yield) as a yellowish oil. R_f 0.65 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −48.1 (*c* 1.10, CH_2Cl_2). ee >99% (HPLC eluent hexane: *i*PrOH = 85:15, flow 1.0 mL/min); $R_{t,1}$ = 5.51 min (*S*), $R_{t,2}$ = 6.05 min (*R*). IR

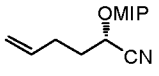
(ATR) 2983, 2352, 1144, 1068, 1014 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.45 (m, 1H), 6.58-6.57 (m, 1H), 6.41-6.40 (m, 1H), 5.56 (s, 1H), 3.30 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.3, 144.0, 117.1, 110.7, 110.1, 102.9, 54.9, 49.6, 24.8, 24.0. HRMS (FAB) *m/z* calcd for $C_{10}H_{14}NO_3$ (M^+): 196.0974, found: 196.0976.

(*S*)-2-(4-Bromophenyl)-2-[(2-methoxypropan-2-yl)oxy]acetonitrile (12)



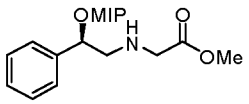
Prepared as described above starting from 4-bromobenzaldehyde (1.00 g, 5.44 mmol) and (*S*)-HNL. The organic layer was washed and afforded **12** (1.54 g, 99% yield) as a colorless oil. R_f 0.60 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –24.4 (*c* 1.44, CH_2Cl_2). ee >99% (HPLC eluent hexane: *i*PrOH = 95:5, flow 1.0 mL/min); $R_{t,1}$ = 14.32 min (*S*), $R_{t,2}$ = 17.27 min (*R*). IR (ATR) 3404, 2932, 2358, 1487, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55-7.52 (m, 2H), 7.37-7.35 (m, 2H), 5.44 (s, 1H), 3.19 (s, 3H), 1.54 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.0, 132.0, 128.4, 128.0, 123.3, 118.6, 102.8, 60.5, 49.7, 24.7, 24.1. HRMS (EI) *m/z* calcd for $C_{12}H_{14}BrNO_2$ (M^+): 283.0208, found: 283.0215.

(*S*)-2-[(2-Methoxypropan-2-yl)oxy]hex-5-enenitrile (13)



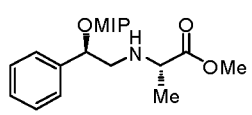
Prepared as described above starting from 4-pentenal (600 mg, 7.14 mmol) and (*S*)-HNL. The organic layer was washed and afforded **13** (1.30 g, 99% yield) as a colorless oil. R_f 0.72 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ –41.5 (*c* 1.36, CH_2Cl_2). IR (ATR) 2950, 2360, 2333, 1215, 1077 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.85-5.75 (ddt, *J* = 6.6, 10.2, 17.0 Hz, 1H), 5.13-5.08 (m, 1H), 5.07-5.04 (m, 1H), 4.44 (dd, *J* = 6.7, 6.7 Hz, 1H), 3.26 (s, 3H), 2.35-2.22 (m, 2H), 1.95-1.84 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.2, 119.8, 116.2, 102.1, 58.8, 49.7, 33.5, 28.7, 24.7, 24.2. HRMS (EI) *m/z* calcd for $C_9H_{14}NO_2$ $(M-CH_3)^+$: 168.1025, found: 168.1026.

Methyl (*R*)-2-(2-(2-methoxypropan-2-yloxy)-2-phenylethylamino)acetate (14)



A solution of cyanohydrin **10** (1.00 g, 4.87 mmol) in dry Et_2O (150 mL) was cooled to –78 °C and DIBALH (24.4 mL of a 1.0 M solution in hexane, 24.4 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min. After quenching with dry MeOH (100 mL), (*S*)-alanine methyl ester hydrochloride (2.50 g, 2.5 equiv) and Et_3N (1.70 mL, 2.5 equiv) were added. The reaction mixture was allowed to warm to rt and stirred for another 2 h. Then the mixture was cooled to 0 °C and $NaBH_4$ (740 mg, 4.0 equiv) was added. After 2 h at 0 °C the mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the product was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 1:3→1:1) to afford **14** (663 mg, 48% yield) as a colorless oil. R_f 0.17 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –79.1 (*c* 1.00, CH_2Cl_2). IR (ATR) 2980, 2937, 2360, 1735, 1201, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 5H), 4.84 (dd, *J* = 5.3, 7.0 Hz, 1H), 3.69 (s, 3H), 3.43 (d, *J* = 17.3 Hz, 1H), 3.37 (d, *J* = 17.2 Hz, 1H), 3.12 (s, 3H), 2.90 (dd, *J* = 7.2, 11.9 Hz, 1H), 2.77 (dd, *J* = 5.2, 11.9 Hz, 1H), 2.10 (br s, 1H), 1.42 (s, 3H), 1.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.5, 142.9, 128.1, 127.2, 126.4, 101.2, 72.6, 56.3, 51.6, 50.6, 49.1, 26.0, 25.0. HRMS (ESI) *m/z* calcd for $C_{15}H_{23}NO_4Na$ $(M+Na)^+$: 304.1525, found: 304.1515.

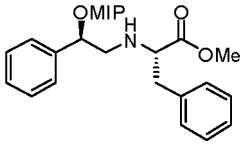
Methyl (*S*)-2({(*R*)-2-[(2-methoxypropan-2-yl)oxy]-2-phenylethyl}amino)propanoate (15)



Prepared as described above starting from cyanohydin **10** (500 mg, 2.44 mmol) and glycine methyl ester hydrochloride (850 mg, 2.5 equiv). Column chromatography (EtOAc/heptane, 1:2→1:1) afforded **15** (233 mg, 32% yield)

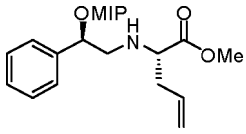
as a colorless oil.R_f 0.76 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –96.2 (*c* 1.21, CH_2Cl_2). IR (ATR) 2984, 2360, 1738, 1206 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.21 (m, 5H), 4.81 (dd, *J* = 4.5, 8.1 Hz, 1H), 3.69 (s, 3H), 3.34 (q, *J* = 6.9 Hz, 1H), 3.14 (s, 3H), 2.85 (dd, *J* = 8.1, 11.9 Hz, 2H), 2.61 (dd, *J* = 4.5, 11.9 Hz, 2H), 1.85 (br s, 1H), 1.42, (s, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.14, (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.8, 143.2, 128.1, 127.1, 126.4, 101.1, 73.2, 56.4, 55.1, 51.6, 49.2, 26.0, 25.1, 18.7. HRMS (ESI) *m/z* calcd for $C_{16}H_{25}NO_4$ $(M+H)^+$: 296.1862, found: 296.1849.

Methyl (*S*)-2-({(*R*)-2-[(2-methoxypropan-2-yl)oxy]-2-phenylethyl}amino)-3-phenylpropanoate (16)



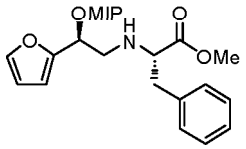
Prepared as described above starting from cyanohydin **10** (500 mg, 2.44 mmol) and (*S*)-phenylalanine methyl ester hydrochloride (2.03 g, 2.5 equiv). Column chromatography (EtOAc/heptane, 1:3→1:1) afforded **16** (403 mg, 44% yield) as a colorless oil. R_f 0.61 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –63.2 (*c* 1.10, CH_2Cl_2). IR (ATR) 2924, 2354, 1734, 1162, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.16 (m, 8H), 7.11-7.09 (m, 2H), 4.76 (dd, *J* = 4.9, 7.6 Hz, 1H), 3.60 (s, 3H), 3.49 (dd, *J* = 6.8, 6.8 Hz, 1H), 3.07 (s, 3H), 2.92-2.87 (m, 3H), 2.55 (dd, *J* = 4.9, 12.0 Hz, 1H), 1.78 (br s, 1H), 1.37 (s, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.6, 143.1, 137.1, 129.0, 128.1, 128.0, 127.0, 126.4, 126.4, 101.0, 73.0, 62.8, 55.0, 51.3, 49.0, 39.4, 26.0, 25.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{29}NO_4$ $(M+H)^+$: 372.2175, found: 372.2170.

Methyl (*S*)-2-({(*R*)-2-[(2-methoxypropan-2-yl)oxy]-2-phenylethyl}amino)pent-4-enoate (17)



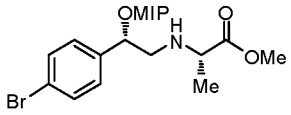
Prepared as described above starting from cyanohydin **10** (282 mg, 1.37 mmol) and (*S*)-allylglycine methyl ester hydrochloride (565 mg, 2.5 equiv). Column chromatography (EtOAc/heptane, 1:4→1:1) afforded **17** (152 mg, 34% yield) as a colorless oil. R_f 0.49 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –85.2 (*c* 1.19, CH_2Cl_2). IR (ATR) 2989, 2941, 2357, 1737, 1204 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.27 (m, 4H), 7.24-7.20 (m, 1H), 5.74-5.64 (m, 1H), 5.07-5.00 (m, 2H), 4.80 (dd, *J* = 4.8, 8.0 Hz, 1H). 3.68 (s, 3H), 3.31 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 8.0, 11.9 Hz, 1H). 2.57 (dd, *J* = 4.8, 11.9 Hz, 1H), 2.40-2.36 (m, 2H), 1.95 (br s, 1H), 1.41 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.6, 143.2, 133.3, 128.0, 127.0, 126.4, 117.7, 101.0, 73.1, 60.9, 55.1, 51.4, 49.1, 37.5, 26.0, 25.0. HRMS (ESI) *m/z* calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$: 344.1838, found: 344.1825.

Methyl (*S*)-2-({(*S*)-2-(2-furyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}amino)-3-phenylpropanoate (18)



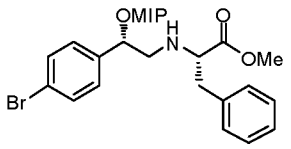
Prepared as described above starting from cyanohydin **11** (500 mg, 2.56 mmol) and (*S*)-phenylalanine methyl ester hydrochloride (1.38 g, 2.5 equiv). Column chromatography (EtOAc/heptane, 1:5→1:1) afforded **18** (90 mg, 10% yield) as a yellowish oil. R_f 0.53 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +23.7 (*c* 1.88, CH_2Cl_2). IR (ATR) 2993, 2946, 1735, 1206, 1147 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.32 (m, 1H), 7.28-7.14 (m, 5H), 6.28 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.19-6.18 (m, 1H), 4.80 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.63 (s, 3H), 3.55 (dd, *J* = 6.3, 7.6 Hz, 1H), 3.01 (s, 3H), 2.98-2.92 (m, 2H), 2.87 (dd, *J* = 7.6, 13.5, 1H), 2.82 (dd, *J* = 6.8, 11.7 Hz, 1H), 1.75 (br s, 1H), 1.32 (s, 3H), 1.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.4, 154.7, 141.5, 137.1, 129.0, 128.3, 126.5, 110.0, 107.1, 101.1, 65.9, 62.9, 51.6, 51.5, 48.9, 39.3, 24.9, 24.8. HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NO_5Na$ $(M+Na)^+$: 384.1787, found: 384.1767.

Methyl (*S*)-2-({(*S*)-2-(4-bromophenyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}amino)propanoate (19)



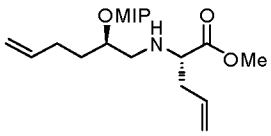
Prepared as described above starting from cyanohydin **12** (500 mg, 1.77 mmol) and (*S*)-alanine methyl ester hydrochloride (617 mg, 2.5 equiv). Column chromatography (EtOAc/heptane, 1:5→1:1) afforded **19** (232 mg, 35% yield) as a colorless oil. R_f 0.37 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +51.5 (*c* 2.59, CH_2Cl_2). IR (ATR) 2997, 2941, 2353, 1737, 1206, 1150, 1071, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.44 (m, 2H), 7.25-7.23 (m, 2H), 4.75 (dd, *J* = 6.3, 6.3 Hz, 1H), 3.68 (s, 3H), 3.35 (q, *J* = 7.0 Hz, 1H), 3.10 (s, 3H), 2.79 (dd, *J* = 6.2, 11.6 Hz, 1H), 2.73 (dd, *J* = 6.3, 11.6 Hz, 1H), 1.65 (br s, 1H), 1.40 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 1H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.6, 142.0, 131.2, 128.3, 120.9, 101.1, 71.9, 56.4, 54.2, 51.5, 49.1, 25.8, 24.9, 18.7. HRMS (ESI) *m/z* calcd for $C_{16}H_{24}BrNO_4$ $(M+H)^+$: 374.0967, found: 374.0966.

Methyl (*S*)-2-({(*S*)-2-(4-bromophenyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}amino)-3-phenylpropanoate (20)



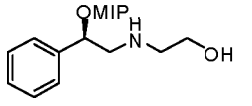
Prepared as described above starting from cyanohydin **12** (500 mg, 1.77 mmol) and (*S*)-phenylalanine methyl ester hydrochloride (953 mg, 2.5 equiv). Column chromatography (EtOAc/heptane, 1:5→1:1) afforded **20** (278 mg, 34% yield) as a colorless oil. R_f 0.61 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +60.8 (*c* 3.02, CH_2Cl_2). IR (ATR) 2944, 2349, 1735, 1205, 1071 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.36 (m, 2H), 7.28-7.19 (m, 3H), 7.14-7.10 (m, 4H), 4.69 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.61 (s, 3H), 3.51 (dd, *J* = 6.1, 7.7 Hz, 1H), 3.00 (s, 3H), 2.94 (dd, *J* = 6.0, 13.5 Hz, 1H), 2.84 (dd, *J* = 7.7, 13.5 Hz, 1H), 2.79 (dd, *J* = 5.7, 11.7 Hz, 1H), 2.66 (dd, *J* = 6.6, 11.7 Hz, 1H), 1.70 (br s, 1H), 1.31 (s, 3H), 1.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.3, 142.0, 137.0, 131.0, 129.0, 128.2, 128.2, 126.5, 120.8, 101.0, 71.6, 62.8, 54.5, 51.4, 49.0, 39.2, 25.7, 24.8. HRMS (ESI) *m/z* calcd for $C_{22}H_{28}BrNO_4$ $(M+H)^+$: 450.1280, found: 450.1276.

Methyl (*S*)-2-({(*R*)-2-[(2-methoxypropan-2-yl)oxy]hex-5-enyl}amino)pent-4-enoate (21)



Prepared as described above starting from cyanohydin **13** (393 mg, 2.15 mmol) and (*S*)-allylglycine methyl ester hydrochloride (700 mg, 2.0 equiv). Column chromatography (EtOAc/heptane, 1:5→1:1) afforded **21** (299 mg, 47% yield) as a colorless oil. R_f 0.54 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −11.5 (*c* 1.14, CH_2Cl_2). IR (ATR) 2991, 2939, 2359, 2337, 1738, 1202 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.86-5.73 (m, 2H), 5.12-4.99 (m, 3H), 4.96-4.93 (m, 1H), 3.86-3.80 (m, 1H), 3.70 (s, 3H), 3.29 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.23 (s, 3H), 2.72 (dd, *J* = 4.8, 11.4 Hz, 1H), 2.49 (dd, *J* = 4.8, 11.7 Hz, 1H), 2.42-2.39 (m, 2H), 2.10-2.04 (m, 2H), 1.78-1.69 (m, 2H), 1.66-1.58 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.8, 138.4, 133.7, 117.5, 114.2, 100.5, 70.0, 61.4, 51.3, 51.0, 48.9, 37.5, 32.3, 29.4, 25.1, 25.0. HRMS (ESI) *m/z* calcd for $C_{16}H_{29}NO_4$ $(M+H)^+$: 300.2174, found: 300.2167.

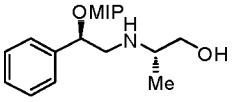
(*R*)-2-(2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethylamino)ethanol (22)



A suspension of $LiALH_4$ (81 mg, 2.0 equiv) in dry THF (20 mL) was cooled to 0 °C and a solution of ester **14** (313 mg, 1.06 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. After quenching with water (95 μL, 5.0 equiv) the mixture was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) to afford **22** (215 mg, 80% yield) as a colorless oil. R_f 0.65 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ −78.5 (*c* 1.10, CH_2Cl_2). IR (ATR) 3321, 2992,

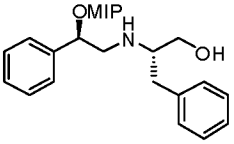
2932, 2362, 1453, 1068, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.23 (m, 5H), 4.89 (dd, *J* = 5.1, 7.5 Hz, 1H), 3.65-3.63 (m, 2H), 3.16 (br s, 2H), 3.13 (s, 3H), 2.93 (dd, *J* = 7.5, 12.4 Hz, 1H), 2.88-2.83 (m, 3H), 1.43 (s, 3H), 1.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.8, 128.3, 127.6, 126.4, 101.7, 71.6, 59.4, 55.5, 50.6, 49.7, 25.2, 25.1. HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_3Na$ $(M+Na)^+$: 276.1576, found: 276.1575.

(*S*)-2-({(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl}amino)propan-1-ol (23)



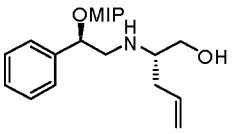
Prepared as described above starting from ester **15** (0.14 g, 0.47 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **23** (0.12 g, 92% yield) as a colorless oil. R_f 0.76 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –47.4 (*c* 1.10, CH_2Cl_2). IR (ATR) 3304, 2920, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.30 (m, 4H), 7.27-7.23 (m, 1H), 4.81 (dd, *J* = 6.3, 6.3 Hz, 1H), 3.53 (dd, *J* = 4.1, 10.6 Hz, 1H), 3.20 (dd, *J* = 7.2, 10.6 Hz, 1H), 3.13 (s, 3H), 2.93 (dd, *J* = 5.6, 12.0 Hz, 1H), 2.82-2.75 (m, 2H), 2.07 (br s, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.0, 128.2, 127.2, 126.5, 101.2, 72.7, 65.2, 54.1, 53.5, 49.3, 25.8, 25.1, 16.9. HRMS (ESI) *m/z* calcd for $C_{15}H_{25}NO_3$ $(M+H)^+$: 268.1913, found: 268.1909.

(*S*)-2-({(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl}amino)-3-phenylpropan-1-ol (24)



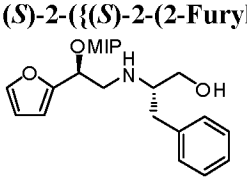
Prepared as described above starting from ester **16** (177 mg, 0.477 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **24** (146 mg, 89% yield) as a colorless oil. R_f 0.49 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –71.0 (*c* 1.15, CH_2Cl_2). IR (ATR) 2928, 2355, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.16 (m, 8H), 7.08-7.06 (m, 2H), 4.74 (dd, *J* = 5.8, 5.8 Hz, 1H), 3.51 (dd, *J* = 3.9, 10.7 Hz, 1H), 3.22 (dd, *J* = 6.0, 10.7 Hz, 1H), 3.06 (s, 3H), 2.88-2.80 (m, 3H), 2.68 (dd, J = 6.9, 13.6 Hz, 1H), 2.63 (dd, J = 6.9, 13.6 Hz, 1H), 1.36 (s, 3H), 1.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.9, 138.4, 129.0, 128.4, 128.1, 127.1, 126.4, 126.2, 101.1, 72.5, 62.4, 60.0, 53.4, 49.1, 37.9, 25.8, 24.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NO_3$ $(M+H)^+$: 344.2226, found: 344.2214.

(*S*)-2-({(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl}amino)pent-4-en-1-ol (25)



Prepared as described above starting from ester **17** (131 mg, 0.408 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **25** (114 mg, 95% yield) as a colorless oil. R_f 0.54 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –44.7 (*c* 1.16, CH_2Cl_2). IR (ATR) 3391, 2983, 2933, 2356, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.28 (m, 4H), 7.25-7.21 (m, 1H), 5.71-5.60 (m, 1H), 5.01-4.99 (m, 1H), 4.97-4.96 (m, 1H), 4.78 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.54 (dd, *J* = 4.1, 10.7 Hz, 1H), 3.25 (dd, *J* = 6.4, 10.7 Hz, 1H), 3.11 (s, 3H), 2.89 (dd *J* = 5.9, 11.8 Hz, 1H), 2.82 (dd, *J* = 6.2, 11.8 Hz, 1H), 2.68-2.62 (m, 1H), 2.15-2.10 (m, 2H), 1.41 (s, 3H), 1.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.9, 134.5, 128.0, 127.1, 126.4, 117.3, 101.1, 72.6, 62.7, 58.0, 53.5, 49.1, 35.8, 25.8, 24.9. HRMS (ESI) *m/z* calcd for $C_{17}H_{27}NO_3$ $(M+H)^+$: 294.2069, found: 294.2054.

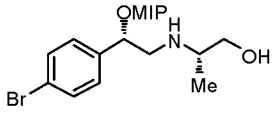
(*S*)-2-({(*S*)-2-(2-Furyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}amino)-3-phenyl-propan-1-ol (26)



Prepared as described above starting from ester **18** (86 mg, 0.24 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **26** (70 mg, 88% yield) as a yellowish oil. R_f 0.46 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ +33.4 (*c* 1.75, CH_2Cl_2). IR (ATR) 3382, 2981, 2927, 2362, 1675, 1129, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.32 (m, 1H), 7.30-7.26 (m, 2H), 7.23-7.19 (m, 1H), 7.17-

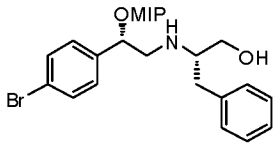
7.15 (m, 2H), 6.29 (dd, J = 1.8, 3.2 Hz, 1H), 6.17-6.16 (m, 1H), 4.77 (dd, J = 5.7, 7.3 Hz, 1H), 3.58 (dd, J = 3.9, 10.8 Hz, 1H), 3.30 (dd, J = 5.3, 10.8 Hz, 1H), 3.01 (s, 3H), 2.99 (dd, J = 7.3, 12.1 Hz, 1H), 2.92-2.85 (m, 1H), 2.84 (dd, J = 5.7, 12.1 Hz, 1H), 2.74 (s, 1H), 2.73 (s, 1H), 1.33 (s, 3H), 1.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.9, 141.5, 138.3, 129.1, 128.5, 126.3, 110.1, 107.1, 101.2, 66.3, 62.2, 59.8, 50.6, 49.1, 38.0, 24.9, 24.9. HRMS (ESI) *m/z* calcd for $C_{19}H_{27}NO_4$ $(M+H)^+$: 334.2018, found: 334.2014.

(*S*)-2-({(*S*)-2-(4-Bromophenyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}amino)-propan-1-ol (27)



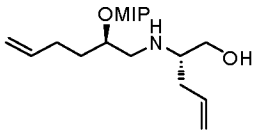
Prepared as described above starting from ester **19** (154 mg, 0.413 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.97:0.03→0.90:0.10) afforded **27** (124 mg, 87% yield) as a colorless oil. R_f 0.35 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ +90.0 (*c* 1.30, CH_2Cl_2). IR (ATR) 3552, 2986, 2920, 2829, 1040 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-.7.44 (m, 2H), 7.24-7.22 (m, 2H), 4.77 (dd, J = 5.0, 7.4 Hz, 1H), 3.52 (dd, J = 4.1, 10.6 Hz, 1H), 3.22 (dd, J = 6.8, 10.6 Hz, 1H), 3.11 (s, 3H), 2.94 (dd, J = 7.4, 12.2 Hz, 1H), 2.76 (m, 1H), 2.65 (dd, J = 5.0, 12.2 Hz, 1H), 2.44 (br s, 2H), 1.41 (s, 3H), 1.14 (s, 3H), 1.03 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.1, 131.2, 128.1, 120.9, 101.3, 72.3, 65.0, 54.1, 53.6, 49.3, 25.7, 25.0, 17.0. HRMS (ESI) *m/z* calcd for $C_{15}H_{24}BrNO_3$ $(M+H)^+$: 346.1018, found: 346.1016.

(*S*)-2-({(*S*)-2-(4-Bromophenyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}amino)-3-phenyl propan-1-ol (28)



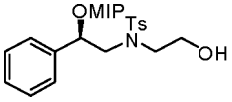
Prepared as described above starting from ester **20** (109 mg, 0.243 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **28** (94.1 mg, 92% yield) as a colorless oil. R_f 0.85 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ +61.4 (*c* 1.04, CH_2Cl_2). IR (ATR) 3404, 2930, 2362, 1718, 1042, 1034 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.38 (m, 2H), 7.30-7.20 (m, 3H), 7.15-7.13 (m, 4H), 4.69 (dd, J = 4.8, 7.3 Hz, 1H), 3.57 (dd, J = 3.9, 10.8 Hz, 1H), 3.30 (dd, J = 5.2, 10.8 Hz, 1H), 3.01 (s, 3H), 2.90-2.84 (m, 1H), 2.80 (dd, J = 7.4, 12.1 Hz, 1H), 2.74-2.67 (m, 3H), 2.27 (br s, 2H), 1.32 (s, 3H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.0, 138.2, 131.2, 129.1, 128.5, 128.1, 126.3, 120.9, 101.2, 72.2, 62.2, 59.9, 53.7, 49.3, 38.0, 25.8, 24.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{28}BrNO_3$ $(M+H)^+$: 422.1331, found: 422.1331.

(*S*)-2-({(*R*)-2-[(2-Methoxypropan-2-yl)oxy]hex-5-enyl}amino)pent-4-en-1-ol (29)



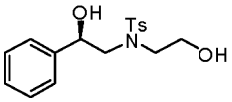
Prepared as described above starting from ester **21** (293 mg, 0.979 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **29** (257 mg, 97% yield) as a colorless oil. R_f 0.43 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ +27.0 (*c* 1.20, CH_2Cl_2). IR (ATR) 3369, 3067, 2988, 2928, 2354, 1639, 1203, 1033, 911 cm^{-1}. 1H NMR ($CDCl_3$, 400 MHz): δ 5.85-5.73 (m, 2H), 5.13-5.07 (m, 2H), 5.04-4.99 (m, 1H), 4.97-4.93 (m, 1H), 3.88-3.82 (m, 1H), 3.60 (dd, J = 4.3, 10.7 Hz, 1H), 3.37 (dd, J = 5.9, 10.7 Hz, 1H), 3.24 (s, 3H), 2.94 (br s, 2H), 2.69-2.64 (m, 3H), 2.24-2.20 (m, 2H), 2.11-2.04 (m, 2H), 1.69-1.62 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 134.7, 117.2, 114.3, 100.6, 70.4, 62.6, 58.3, 50.4, 48.9, 35.8, 32.6, 29.2, 25.1, 24.8. HRMS (ESI) *m/z* calcd for $C_{15}H_{29}NO_3$ $(M+H)^+$: 272.2226, found: 272.2210.

(*R*)-*N*-(2-Hydroxyethyl)-*N*-{2-[(2-methoxypropan-2-yl)oxy]-2-phenylethyl}-4-methylbenzenesulfonamide (30)



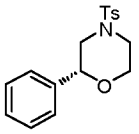
To a solution of alcohol **22** (155 mg, 0.612 mmol) in dry DCM (20 mL) were added Et_3N (170 µL, 2.0 equiv) and *p*-toluenesulfonyl chloride (128 mg, 1.1 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. Then the mixture was allowed to warm to rt. After 5 h the mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the product was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) to afford **30** (204 mg, 82% yield) as a colorless oil. R_f 0.67 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –87.2 (*c* 1.34, CH_2Cl_2). IR (ATR) 3421, 2937, 2351, 1348, 1159, 705, 550 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.65 (m, 2H), 7.38-7.27 (m, 7H), 5.30 (dd, *J* = 4.7, 8.9 Hz, 1H), 4.14 (dd, *J* = 5.2, 8.9 Hz, 1H), 3.88-3.81 (m, 1H), 3.76-3.69 (m, 1H), 3.48 (ddd, *J* = 2.8, 4.8, 14.4 Hz, 1H), 3.21-3.17 (m, 2H), 3.15 (s, 3H), 2.83 (ddd, *J* = 2.7, 8.2, 14.4 Hz, 1H), 2.40 (s, 3H), 1.53 (s, 3H), 1.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.6, 141.9, 134.9, 129.7, 128.4, 127.7, 127.4, 126.6, 102.3, 74.3, 62.5, 57.9, 54.5, 49.8, 25.8, 25.0, 21.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NO_5SNa$ $(M+Na)^+$: 430.1664, found: 430.1687.

(*R*)-*N*-(2-Hydroxy-2-phenylethyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (31)



A solution of alcohol **30** (135 mg, 0.332 mmol) in THF (6 mL) was acidified with aqueous HCl (0.2 M solution) to pH 2-3. The reaction mixture was stirred at rt for 1 h. Then the mixture was diluted with water (18 mL) and neutralized with saturated aqueous $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **31** (111 mg, 100% yield) as a colorless oil. R_f 0.45 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –65.5 (*c* 1.03, CH_2Cl_2). IR (ATR) 3343, 2925, 1335, 1159, 700, 550 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.66 (m, 2H), 7.39-7.26 (m, 7H), 5.14 (dd, *J* = 2.3, 9.9 Hz, 1H), 4.31 (br s, 1H), 4.00 (br s, 1H), 3.94-3.89 (m, 1H), 3.83-3.80 (m, 1H), 3.51 (ddd, *J* = 3.3, 5.9, 14.7 Hz, 1H), 3.39 (dd, *J* = 2.6, 14.9 Hz, 1H), 3.07-3.00 (m, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7, 141.1, 135.0, 129.7, 128.5, 127.9, 127.2, 125.8, 74.1, 62.1, 58.8, 53.5, 21.4. HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_4SNa$ $(M+Na)^+$: 358.1089, found: 358.1102.

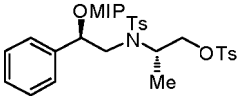
(*R*)-2-Phenyl-4-(4-methylbenzenesulfonyl)morpholine (32)



A solution of alcohol **31** (0.11 g, 0.32 mmol) in THF (15 mL) was cooled to 0 °C and NaH (32 mg of 60% NaH in oil, 2.5 equiv) was added. The resulting mixture was allowed to warm to rt and stirred for 1 h. Then the mixture was cooled to 0 °C and 1-(*p*-Toluenesulfonyl)imidazole (78 mg, 1.1 equiv) was added. The resulting mixture was allowed to warm to rt and stirred overnight. The reaction mixture was cooled to 0 °C again and quenched by the dropwise addition of saturated aqueous NH_4Cl. The resulting solution was diluted with EtOAc (30 mL) and washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine (2 × 20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography (EtOAc/heptane, 1:5→1:1) afforded **32** (83 mg, 83% yield) as a colorless oil. R_f 0.53 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ –106.7 (*c* 1.11, CH_2Cl_2). IR (ATR) 2850, 1349, 1165, 554 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.60 (m, 2H), 7.35-7.26 (m, 7H), 4.59 (dd, *J* = 2.6, 10.3 Hz, 1H), 4.06 (ddd, *J* = 1.3, 3.4, 11.6 Hz, 1H), 3.84 (dt, *J* = 2.7, 11.6 Hz, 1H), 3.78-3.74 (m, 1H), 3.64-3.60 (m, 1H), 2.49 (dt, *J* = 3.4, 11.6 Hz, 1H), 2.41 (s, 3H), 2.24 (dd, *J* = 10.3, 11.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz):

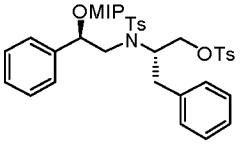
δ 143.8, 138.5, 132.0, 129.7, 128.4, 128.1, 127.7, 125.9, 77.2, 66.1, 51.8, 45.3, 21.4. HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_3SNa$ ($M+Na^+$: 340.0983, found: 340.0973.

(*S*)-2-(*N*-{(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl}-4-methylbenzenesulfonamido)-propyl-4-methylbenzenesulfonate (33)



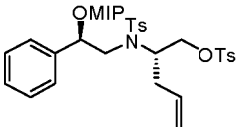
To a solution of alcohol **23** (86 mg, 0.32 mmol) in pyridine (2 mL) were added Et_3N (0.36 mL, 8.0 equiv) and *p*-toluenesulfonyl chloride (0.25 g, 4.0 equiv) at rt. Upon addition of *p*-toluenesulfonyl chloride the solution turned red. The reaction mixture was stirred at rt overnight. Then ethylenediamine (86 μL, 4.0 equiv) was added. After 2.5 h the mixture was diluted with EtOAc (10 mL). The resulting solution was washed sequentially with saturated aqueous NH_4Cl (10 mL) and a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine (10 mL). The organic layer was separated and the aqueous washes were combined and extracted with EtOAc (15 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 1:4→1:2) to afford **33** (0.15 g, 80% yield) as a colorless oil. R_f 0.52 (EtOAc/heptane, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.59 (m, 4H), 7.33-7.18 (m, 9H), 5.13 (dd, *J* = 6.0, 8.3 Hz, 1H) 3.89-3.80 (m, 1H), 3.31 (dd, *J* = 6.0, 14.9 Hz, 1H), 3.26 (dd, *J* = 5.0, 9.8 Hz, 1H), 3.05, (s, 3H), 2.92 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.87 (dd, *J* = 8.3, 14.9 Hz, 1H), 2.47 (s, 3H), 2.42 (s, 3H), 1.42 (s, 3H), 1.15 (s, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

(*S*)-2-(*N*-{(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl}-4-methylbenzenesulfonamido)-3-phenylpropyl-4-methylbenzenesulfonate (34)



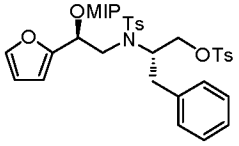
Prepared as described above starting from alcohol **24** (42 mg, 0.12 mmol). Column chromatography (EtOAc/heptane, 1:4→1:1) afforded **34** (59 mg, 74% yield) as a colorless oil. R_f 0.46 (EtOAc/heptane, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.54-7.51 (m, 2H), 7.50-7.47 (m, 2H), 7.30-7.13 (m, 12H), 6.90-6.88 (m, 2H), 5.05 (dd, *J* = 6.8, 6.8 Hz, 1H), 3.95-3.88 (m, 1H), 3.77 (dd, *J* = 6.4, 10.5 Hz, 1H), 3.37 (dd, *J* = 5.2, 10.1 Hz, 1H), 3.33 (dd, *J* = 5.3, 5.3 Hz, 1H), 3.14 (dd, *J* = 6.6, 15.5 Hz, 1H), 2.99 (s, 3H), 2.92 (dd, *J* = 8.9, 14.1 Hz, 1H), 2.79 (dd, *J* = 6.1, 14.1 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 1.40 (s, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.7, 143.4, 142.1, 136.9, 136.4, 129.9, 129.7, 129.6, 129.5, 128.9, 128.8, 128.7, 128.5, 128.3, 127.9, 127.8, 127.6, 127.4, 127.2, 126.8, 126.5, 125.8, 101.5, 72.6, 69.2, 60.0, 53.0, 49.3, 36.9, 25.8, 25.1, 21.6, 21.4.

(*S*)-2-(*N*-{(*R*)-2-[(2-Methoxypropan-2-yl)oxy]-2-phenylethyl}-4-methylbenzenesulfonamido)pent-4-enyl-4-methylbenzenesulfonate (35)



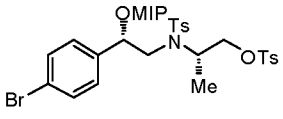
Prepared as described above starting from alcohol **25** (110 mg, 0.375 mmol). Column chromatography (EtOAc/heptane, 1:6→1:1) afforded **35** (191 mg, 85% yield) as a colorless oil. R_f 0.62 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –27.4 (*c* 1.50, CH_2Cl_2). IR (ATR) 2988, 2366, 1348, 1176, 1157 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.61 (m, 2H), 7.60-7.59 (m, 2H), 7.32-7.21 (m, 9H), 5.14-5.04 (m, 2H), 4.86 (dd, *J* = 1.6, 17.1 Hz, 1H), 4.77 (dd, *J* = 1.6, 10.1 Hz, 1H), 3.71-3.64 (m, 1H), 3.54 (dd, *J* = 5.6, 10.1 Hz, 1H), 3.40 (dd, *J* = 6.2, 15.1 Hz, 1H), 3.06-2.96 (m, 5H), 2.46 (s, 3H), 2.42 (s, 3H), 2.33-2.26 (m, 1H), 2.08-2.01 (m, 1H), 1.41 (s, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.7, 143.6, 142.0, 136.2, 133.1, 132.5, 129.6, 129.5, 128.2, 127.8, 127.6, 127.5, 127.2, 118.0, 101.4, 72.3, 70.0, 57.7, 52.6, 49.2, 34.3, 25.7, 25.0, 21.6, 21.4. HRMS (ESI) *m/z* calcd for $C_{31}H_{39}NO_7S_2Na$ $(M+Na)^+$: 624.2066, found: 624.2062.

(*S*)-2-(*N*-{(*S*)-2-(2-Furyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}-4-methylbenzenesulfonamido)-3-phenylpropyl-4-methylbenzenesulfonate (36)



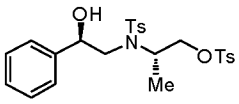
Prepared as described above starting from alcohol **26** (64 mg, 0.19 mmol). Column chromatography (EtOAc/heptane, 1:7→1:1) afforded **36** (86 mg, 70% yield) as a colorless oil. R_f 0.59 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +4.5 (*c* 1.08, CH_2Cl_2). IR (ATR) 2991, 1345, 1176, 1155 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60-7.55 (m, 4H), 7.38-7.37 (m, 1H), 7.26-7.20 (m, 4H), 7.14-7.09 (m, 3H), 6.85-6.83 (m, 2H), 6.30 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.25 (dd, *J* = 0.8, 3.3 Hz, 1H), 5.16 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.05 (dd, *J* = 6.3, 9.6 Hz, 1H), 4.01-3.91 (m, 2H), 3.42 (dd, *J* = 6.8, 15.3 Hz, 1H), 3.34 (dd, *J* = 7.2, 15.3 Hz, 1H), 2.98 (s, 3H), 2.44 (s, 3H), 2.42-2.33 (m, 2H), 2.40 (s, 3H), 1.42 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5, 144.7, 143.5, 141.7, 136.7, 136.4, 132.4, 129.6, 129.5, 128.6, 128.5, 127.8, 127.3, 126.5, 110.4, 108.9, 101.6, 68.8, 65.9, 59.3, 49.1, 49.0, 36.1, 24.9, 24.8, 21.5, 21.4. HRMS (ESI) *m/z* calcd for $C_{33}H_{39}NO_8S_2Na$ $(M+Na)^+$: 664.2015, found: 664.1998.

(*S*)-2-(*N*-{(*S*)-2-(4-Bromophenyl)-2-[(2-methoxypropan-2-yl)oxy]ethyl}-4-methylbenzenesulfonamido)propyl-4-methylbenzenesulfonate (37)



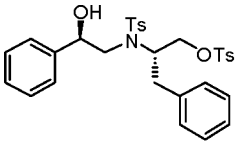
Prepared as described above starting from alcohol **27** (116 mg, 0.336 mmol). Column chromatography (EtOAc/heptane, 1:5→1:1) afforded **37** (194 mg, 88% yield) as a colorless oil. R_f 0.66 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +56.2 (*c* 0.98, CH_2Cl_2). IR (ATR) 3507, 2984, 1341, 1175, 1155, 551 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.61-7.59 (m, 2H), 7.43-7.41 (m, 2H), 7.37-7.35 (m, 2H), 7.28-7.20 (m, 4H), 5.10 (dd, *J* = 5.0, 8.1 Hz, 1H), 4.09-4.00 (m, 3H), 3.04-2.93 (m, 5H), 2.46 (s, 3H), 2.39 (s, 3H), 1.38 (s, 3H), 1.11 (s, 3H), 0.65 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.9, 143.6, 141.3, 136.1, 132.5, 131.2, 129.7, 129.6, 128.5, 127.7, 127.0, 121.2, 101.5, 72.2, 71.2, 52.4, 51.0, 49.3, 25.7, 24.8, 21.5, 21.3, 14.0. HRMS (ESI) *m/z* calcd for $C_{29}H_{36}BrNO_7S_2Na$ $(M+Na)^+$: 676.1014, found: 676.0986.

(*S*)-2-{*N*-[(*R*)-2-Hydroxy-2-phenylethyl]-4-methylbenzenesulfonamido}propyl-4-methylbenzenesulfonate (40)



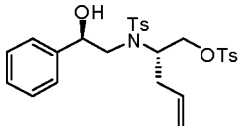
A solution of alcohol **33** (93 mg, 0.16 mmol) in THF (3 mL) was acidified with aqueous HCl (0.2 M solution) to pH 2-3. The reaction mixture was stirred at rt for 1 h. Then the mixture was diluted with water (9 mL) and neutralized with saturated aqueous $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **40** (73 mg, 90% yield) as a colorless oil. R_f 0.37 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −10.6 (*c* 1.02, CH_2Cl_2). IR (ATR) 3503, 2920, 1336 1175, 1152 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.67 (m, 4H), 7.35-7.23 (m, 9H), 4.85-4.83 (m, 1H), 4.19-4.06 (m, 2H), 3.88 (dd, *J* = 5.9, 10.0 Hz, 1H), 3.27 (br s, 1H), 3.24 (dd, *J* = 9.2, 15.6 Hz, 1H), 3.11 (dd, *J* = 3.3, 15.6 Hz, 1H), 2.44 (s, 3H), 2.41 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.1, 143.9, 141.5, 136.3, 132.3, 129.9, 129.8, 128.5, 127.9, 127.2, 125.8, 73.3, 71.5, 53.2, 52.5, 21.6, 21.4, 14.7. HRMS (ESI) *m/z* calcd for $C_{25}H_{29}NO_6S_2Na$ $(M+Na)^+$: 526.1334, found: 526.1327.

(*S*)-2-{*N*-[(*R*)-2-Hydroxy-2-phenylethyl]-4-methylbenzenesulfonamido}-3-phenylpropyl-4-methylbenzenesulfonate (41)



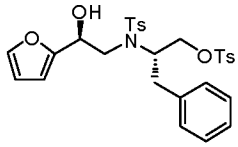
Prepared as described above starting from alcohol **34** (40 mg, 0.061 mmol). Extraction of the mixture afforded **41** (35 mg, 98% yield) as a colorless oil. R_f 0.32 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –13.8 (*c* 1.00, CH_2Cl_2). IR (ATR) 3512, 2958, 2358, 1337, 1176, 1158 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.63 (m, 2H), 7.63-7.61 (m, 2H), 7.37-7.19 (m, 12H), 7.03-7.01 (m, 2H), 4.86-4.82 (m, 1H), 4.23-4.16 (m, 2H), 4.02-3.97 (m, 1H), 3.25-3.23 (m, 2H), 3.15-3.16 (m, 1H), 2.95 (dd, *J* = 8.5, 13.9 Hz, 1H), 2.82 (dd, *J* = 5.7, 13.9 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.1, 143.9, 141.5, 136.6, 136.3, 132.1, 129.9, 129.7, 128.9, 128.7, 128.5, 127.9, 127.4, 126.9, 125.8, 73.2, 69.3, 59.8, 53.5, 36.2, 21.6, 21.5. HRMS (ESI) *m/z* calcd for $C_{31}H_{33}NO_6S_2Na$ $(M+Na)^+$: 602.1647, found: 602.1621.

(*S*)-2-{*N*-[(*R*)-2-Hydroxy-2-phenylethyl]-4-methylbenzenesulfonamido}pent-4-enyl-4-methylbenzenesulfonate (42)



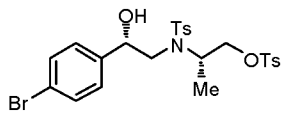
Prepared as described above starting from alcohol **35** (190 mg, 0.316 mmol). Extraction of the mixture afforded **42** (159 mg, 95% yield) as a colorless oil. R_f 0.47 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –26.5 (*c* 1.72, CH_2Cl_2). IR (ATR) 3520, 2920, 2358, 1339, 1173, 1153 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.56 (m, 4H), 7.23-7.15 (m, 9H), 5.32 (ddt, *J* = 6.9, 10.1, 17.0 Hz, 1H), 4.89-4.81 (m, 2H), 4.78 (dd, *J* = 4.0, 8.2 Hz, 1H), 4.05-4.01 (m, 1H), 3.96-3.89 (m, 1H), 3.87-3.83 (m, 1H), 3.17-2.91 (m, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 2.30-2.24 (m, 1H), 2.17-2.09 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 143.8, 141.4, 136.0, 133.0, 132.0, 129.7, 129.6, 128.3, 127.7, 127.3, 125.6, 118.5, 73.0, 69.8, 57.5, 53.1, 33.8, 21.4, 21.3. HRMS (ESI) *m/z* calcd for $C_{27}H_{31}NO_6S_2Na$ $(M+Na)^+$: 552.1491, found: 552.1468.

(*S*)-2-{*N*-[(*S*)-2-(2-Furyl)-2-hydroxyethyl]-4-methylbenzenesulfonamido}-3-phenylpropyl-4-methylbenzenesulfonate (43)



Prepared as described above starting from alcohol **36** (82 mg, 0.13 mmol). Extraction of the mixture afforded **43** (67 mg, 92% yield) as a colorless oil. R_f 0.55 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +5.0 (*c* 1.00, CH_2Cl_2). IR (ATR) 3512, 2918, 1169, 1148 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.62 (m, 2H), 7.62-7.59 (m, 2H), 7.39-7.38 (m, 1H), 7.27-7.17 (m, 7H), 7.02-6.99 (m, 2H), 6.35 (dd, *J* = 1.8, 3.3 Hz, 1H), 6.30 (m, 1H), 4.97 (dd, *J* = 4.1, 8.1 Hz, 1H), 4.25-.4.16 (m, 2H), 4.03-3.99 (m, 1H), 3.47 (dd, *J* = 3.6, 15.1 Hz, 1H), 3.41 (dd, *J* = 7.6, 15.1 Hz, 1H), 2.98 (br s, 1H), 2.87 (dd, *J* = 5.6, 13.9 Hz, 1H), 2.79 (dd, *J* = 8.8, 13.9 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.7, 144.9, 143.7, 142.2, 136.5, 136.3, 132.3, 129.7, 129.7, 128.8, 128.7, 127.9, 127.4, 126.8, 110.3, 107.0, 68.7, 67.4, 59.4, 49.9, 36.5, 21.6, 21.5. HRMS (ESI) *m/z* calcd for $C_{29}H_{31}NO_7S_2Na$ $(M+Na)^+$: 592.1440, found: 592.1437.

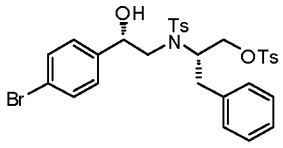
(*S*)-2-{*N*-[(*S*)-2-(4-Bromophenyl)-2-hydroxyethyl]-4-methylbenzenesulfonamido}propyl-4-methylbenzenesulfonate (44)



Prepared as described above starting from alcohol **37** (190 mg, 0.291 mmol). Extraction of the mixture afforded **44** (169 mg, 100% yield) as a colorless oil. R_f 0.65 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +26.5 (*c* 1.33, CH_2Cl_2). IR (ATR) 3516, 2918, 2359, 1336, 1172, 1151, 553 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.70 (m, 2H), 7.67-7.64 (m, 2H), 7.45-7.41 (m, 2H), 7.33-7.31 (m, 2H), 7.27-7.25 (m, 2H), 7.22-7.20 (m,

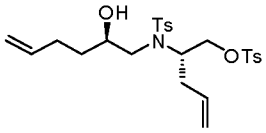
2H), 4.94 (dd, J = 2.3, 9.3 Hz, 1H), 4.17-4.10 (m, 2H), 4.05-3.99 (m, 1H), 3.20 (dd, J = 2.5, 15.5 Hz, 1H), 2.99 (br s, 1H), 2.96 (dd, J = 9.4, 15.5 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 143.8, 140.6, 136.2, 132.3, 131.4, 129.7, 129.7, 127.7, 127.4, 127.0, 121.4, 72.7, 70.9, 52.7, 52.1, 21.5, 21.3, 14.8. HRMS (ESI) *m/z* calcd for $C_{25}H_{28}BrNO_6S_2Na$ $(M+Na)^+$: 604.0439, found: 604.0428.

(*S*)-2-{*N*-[(*S*)-2-(4-Bromophenyl)-2-hydroxyethyl]-4-methylbenzenesulfonamido}-3-phenylpropyl-4-methylbenzenesulfonate (45)



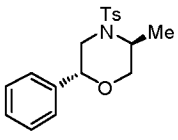
Prepared as described above starting from alcohol **38** (59 mg, 0.14 mmol). Column chromatography (EtOAc/toluene, 1:9→1:1) afforded **45** (88 mg, 96% yield) as a colorless oil. R_f 0.60 (EtOAc/toluene, 1:4). $[\alpha]_D^{20}$ +19.6 (*c* 1.12, CH_2Cl_2). IR (ATR) 3507, 2921, 1336, 1177, 1150, 551 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.59 (m, 4H), 7.48-7.46 (m, 2H), 7.27-7.17 (m, 9H), 6.99-6.97 (m, 2H), 4.95 (dd, J = 2.0, 9.3 Hz, 1H), 4.26-4.19 (m, 2H), 4.10-4.04 (m, 1H), 3.27 (dd, J = 2.0, 15.6 Hz, 1H), 3.13 (dd, J = 9.5, 15.5 Hz, 1H), 2.87 (dd, J = 5.4, 13.9 Hz, 1H), 2.81 (dd, J = 8.5, 14.0 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 1.43 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 143.8, 140.5, 136.4, 136.3, 132.2, 131.6, 129.8, 129.7, 128.7, 128.6, 127.8, 127.4, 127.2, 126.8, 121.6, 72.6, 68.9, 59.4, 53.1, 36.4, 30.2, 21.6, 21.4. HRMS (ESI) *m/z* calcd for $C_{31}H_{32}BrNO_6S_2Na$ $(M+Na)^+$: 680.0752, found: 680.0739.

(*S*)-2-{*N*-[(*R*)-2-Hydroxyhex-5-enyl]-4-methylbenzenesulfonamido}pent-4-enyl-4-methylbenzenesulfonate (46)



Prepared as described above starting from alcohol **39** (247 mg, 0.911 mmol). Column chromatography (EtOAc/toluene, 1:7→1:1) afforded **46** (370 mg, 80% yield) as a colorless oil. R_f 0.50 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −1.6 (*c* 1.12, CH_2Cl_2). IR (ATR) 3540, 2924, 1175, 1156, 551 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.66 (m, 4H), 7.33-7.31 (m, 2H), 7.28-7.26 (m, 2H), 5.78 (ddt, J = 6.6, 10.2, 16.9 Hz, 1H), 5.43 (ddt, J = 6.9, 10.1, 17.1 Hz, 1H), 5.04-4.92 (m, 4H), 4.17-4.12 (m, 1H), 4.08-4.01 (m, 2H), 3.81-3.75 (m, 1H), 3.30 (br s, 1H), 3.10 (dd, J = 2.5, 15.4 Hz, 1H), 2.91 (dd, J = 9.1, 15.5 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.30-2.13 (m, 3H), 2.12-2.03 (m, 1H), 1.45-1.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 143.6, 137.9, 136.5, 132.9, 132.3, 129.7, 129.6, 127.8, 127.3, 118.5, 114.9, 69.8, 69.2, 57.2, 51.1, 34.2, 33.8, 29.5, 21.5, 21.4. HRMS (ESI) *m/z* calcd for $C_{25}H_{33}NO_6S_2$ $(M+H)^+$: 508.1828, found: 508.1839.

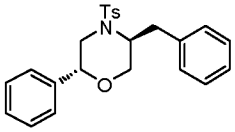
(2*R*,5*S*)-5-Methyl-4-(4-methylbenzenesulfonyl)-2-phenylmorpholine (47)



A solution of tosylate **40** (48 mg, 0.10 mmol) in THF (5 mL) was cooled to 0 °C and NaH (3.4 mg of 60% NaH in oil, 1.5 equiv) was added. The resulting mixture was allowed to warm to rt and stirred for 1 h. Then the mixture was cooled to 0 °C and quenched by the dropwise addition of saturated aqueous NH_4Cl (1 mL). The resulting solution was diluted with EtOAc (30 mL) and washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine (2 × 20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to afford **47** (32 mg, 96% yield) as a colorless oil. R_f 0.44 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ −88.2 (*c* 1.45, CH_2Cl_2). IR (ATR) 2855, 1349, 1166 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.63 (m, 2H), 7.35-7.25 (m, 7H), 4.69 (dd J = 2.3, 9.1 Hz, 1H), 3.94 (dd, J = 2.6, 12.1 Hz, 1H), 3.81 (dd, J = 3.2, 11.7 Hz, 1H), 3.47 (dd, J = 9.0, 11.6 Hz, 1H), 2.92-2.84 (m, 1H), 2.66 (dd, J = 9.2, 12.0 Hz, 1H), 2.43 (s, 3H),

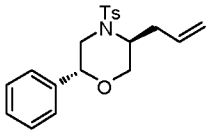
1.36 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7, 138.4, 133.7, 129.7, 128.4, 128.1, 127.6, 126.1, 77.1, 71.7, 52.3, 51.9, 21.4, 16.1. HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_3S$ $(M+H)^+$: 332.1320, found: 332.1309.

(2*R*,5*S*)-5-Benzyl-4-(4-methylbenzenesulfonyl)-2-phenylmorpholine (48)



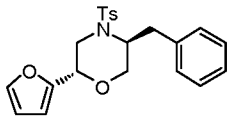
Prepared as described above starting from tosylate **41** (34 mg, 0.058 mmol). Column chromatography (EtOAc/heptane, 1:4→1:1) afforded **48** (24 mg, 99% yield) as a colorless oil. R_f 0.56 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –36.9 (*c* 1.71, CH_2Cl_2). IR (ATR) 2925, 2360, 1344, 1164, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.71 (m, 2H), 7.38-7.16 (m, 12H), 4.91 (dd, J = 3.7, 5.7 Hz, 1H), 3.84 (dd, J = 3.7, 12.6 Hz, 1H), 3.56 (dd, J = 2.3, 11.7 Hz, 1H), 3.53-3.47 (m, 2H), 3.42 (dd, J = 4.2, 11.6 Hz, 1H), 3.14 (dd, J = 3.6, 13.3 Hz, 1H), 3.04 (dd, J = 11.1, 13.3 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.8, 138.2, 137.6, 135.4, 129.8, 129.3, 128.6, 128.4, 127.9, 127.5, 126.7, 126.6, 74.3, 63.8, 56.6, 46.4, 35.2, 21.5. HRMS (ESI) *m/z* calcd for $C_{24}H_{25}NO_3S$ $(M+H)^+$: 408.1633, found: 408.1623.

(2*R*,5*S*)-5-Allyl-4-(methylbenzenesulfonyl)-2-phenylmorpholine (49)



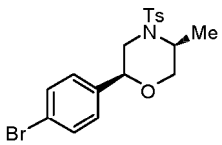
Prepared as described above starting from tosylate **42** (159 mg, 0.300 mmol). Column chromatography (EtOAc/heptane, 1:7→1:1) afforded **49** (104 mg, 97% yield) as a colorless oil. R_f 0.62 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –15.5 (*c* 0.94, CH_2Cl_2). IR (ATR) 2919, 2855, 2358, 2381, 1347, 1166 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.63 (m, 2H), 7.37-7.26 (m, 7H), 5.82-5.72 (m, 1H), 5.11-5.07 (m, 2H), 4.77 (dd, J = 3.3, 6.9 Hz, 1H), 3.81 (dd, J = 3.4, 12.4 Hz, 1H), 3.79 (dd, J = 3.2, 11.9 Hz, 1H), 3.56 (dd, J = 6.2, 11.9 Hz, 1H), 3.18-3.11 (m, 2H), 2.71-2.63 (m, 1H), 2.55-2.49 (m, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7, 138.2, 134.5, 133.6, 129.7, 128.3, 127.8, 127.4, 126.4, 118.1, 75.1, 66.1, 54.8, 48.4, 33.6, 21.4. HRMS (ESI) *m/z* calcd for $C_{20}H_{24}NO_3S$ $(M+H)^+$: 358.1477, found: 358.1462.

(2*S*,5*S*)-5-Benzyl-2-(2-furyl)-4-(4-methylbenzenesulfonyl)morpholine (50)



Prepared as described above starting from tosylate **43** (41 mg, 0.072 mmol). Column chromatography (EtOAc/heptane, 1:7→1:1) afforded0 **5** (21 mg, 73% yield) as a colorless oil. R_f 0.59 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ –11.7 (*c* 1.05, CH_2Cl_2). IR (ATR) 2921, 2854, 2357, 500 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.61 (m, 2H), 7.42-7.41 (m, 1H), 7.30-7.19 (m, 7H), 6.38-6.36 (m, 2H), 4.47 (dd, J = 3.0, 11.2 Hz, 1H), 4.10-4.06 (m, 1H), 3.84-3.77 (m, 2H), 3.59 (ddd, J = 1.0, 3.0, 11.8 Hz, 1H), 3.48 (dd, J = 11.2, 13.4 Hz, 1H), 3.12 (dd, J = 10.2, 13.2 Hz, 1H), 2.79 (dd, J = 5.1, 13.2 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.1, 143.5, 142.7, 137.6, 137.3, 129.8, 129.4, 128.6, 127.1, 126.6, 110.2, 107.9, 70.9, 67.4, 54.0, 43.2, 34.1, 21.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{23}NO_4S$ $(M+H)^+$: 398.1426, found: 398.1420.

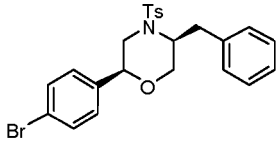
(2*S*,5*S*)-2-(4-Bromophenyl)-5-methyl-4-(4-methylbenzenesulfonyl)morpholine (51)



Prepared as described above starting from tosylate **44** (169 mg, 0.259 mmol). Column chromatography (EtOAc/heptane, 1:6→1:1) afforded **51** (100 mg, 94% yield) as a colorless oil. R_f 0.58 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +72.1 (*c* 1.00, CH_2Cl_2). IR (ATR) 2971, 2855, 2355, 1341, 1154, 554 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.67 (m, 2H), 7.49-7.46 (m, 2H), 7.31-7.28 (m, 2H), 7.23-7.20 (m, 2H), 4.37 (dd, J = 3.0, 10.9 Hz, 1H), 4.09-4.03 (m, 1H), 3.81 (ddd, J = 0.5, 2.7, 11.4 Hz, 1H), 3.76 (dd, J = 1.4, 11.5 Hz, 1H), 3.72 (ddd, J = 0.6, 3.1, 13.0 Hz, 1H), 2.94 (dd, J = 10.9, 13.1 Hz, 1H), 2.41 (s, 3H), 1.14 (d, J

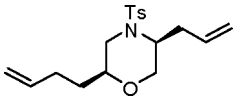
= 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.4, 137.7, 137.2, 131.5, 129.7, 127.5, 126.9, 122.0, 77.0, 71.5, 48.0, 45.7, 21.4, 13.4. HRMS (ESI) *m/z* calcd for $C_{18}H_{20}BrNO_3S$ $(M+H)^+$: 410.0426, found: 410.0436.

(2*S*,5*S*)-5-Benzyl-2-(4-bromophenyl)-4-(4-methylbenzenesulfonyl)morpholine (52)



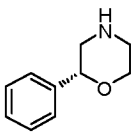
Prepared as described above starting from tosylate **45** (64 mg, 0.097 mmol). Column chromatography (EtOAc/heptane, 1:9→1:4) afforded **52** (44 mg, 93% yield) as a colorless oil. R_f 0.81 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +22.9 (*c* 1.35, CH_2Cl_2). IR (ATR) 2859, 2360, 1346, 1166, 556 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.61 (m, 2H), 7.52-7.49 (m, 2H), 7.32-7.19 (m, 9H), 4.41 (dd, *J* = 3.0, 10.9 Hz, 1H), 4.11-4.06 (m, 1H), 3.84 (m, 1H), 3.76 (dd, *J* = 3.0, 13.5 Hz, 1H), 3.62 (ddd, *J* = 0.9, 3.0, 11.8 Hz, 1H), 3.11-3.04 (m, 2H), 2.72 (dd, *J* = 5.1, 13.2 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ143.5, 137.7, 137.5, 137.3, 131.6, 129.8, 129.4, 128.6, 127.6, 127.0, 126.6, 122.1, 76.9, 67.6, 53.8, 46.5, 33.9, 21.4. HRMS (ESI) *m/z* calcd for $C_{24}H_{24}BrNO_3S$ $(M+H)^+$: 486.0739, found: 486.0757.

(2*S*,5*S*)-5-Allyl-2-(but-3-enyl)-4-(4-methylbenzenesulfonyl)morpholine (53)



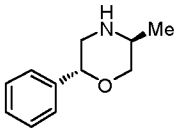
Prepared as described above starting from tosylate **46** (289 mg, 0.570 mmol). Column chromatography (EtOAc/heptane, 1:8→1:1) afforded **53** (158 mg, 83% yield) as a colorless oil. R_f 0.65 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ +21.0 (*c* 1.31, CH_2Cl_2). IR (ATR) 2918, 2853, 2358, 1339, 1161, 680, 552 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.68 (m, 2H), 7.30-7.28 (m, 2H), 5.80-5.63 (m, 2H), 5.08-4.94 (m, 4H), 3.82-3.77 (m, 1H), 3.75-3.72 (m, 1H), 3.58 (dd, *J* = 2.6, 13.4 Hz, 1H), 3.41 (ddd, *J* = 1.0, 3.0, 11.6 Hz, 1H), 3.26-3.19 (m, 1H), 2.83 (dd, *J* = 11.0, 13.4 Hz, 1H), 2.50-2.44 (m, 1H), 2.41 (s, 3H), 2.23-2.02 (m, 3H), 1.60-1.51 (m, 1H), 1.48-1.39 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.1, 137.8, 137.4, 134.0, 129.6, 126.8, 117.8, 114.9, 74.3, 67.4, 52.1, 44.9, 32.3, 31.9, 28.8, 21.2. HRMS (ESI) *m/z* calcd for $C_{18}H_{25}NO_3S$ $(M+H)^+$: 336.1633, found: 336.1618.

(*R*)-2-Phenylmorpholine (54)



A solution of SmI_2 (9.5 mL of a 0.1 M solution in THF, 0.95 mmol, 10 equiv) and water (51 µL, 30 equiv) were added to morpholine **32** (30 mg, 0.095 mmol) under an argon atmosphere. Subsequently pyrrolidine (0.16 mL, 20 equiv) was added. The reaction mixture turned white instantaneously upon addition of amine. The resulting mixture was quenched by blowing air through the mixture. The mixture was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) to afford **54** (20 mg, 80% yield) as a colorless oil. R_f 0.19 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ −13.3 (*c* 0.06, CH_2Cl_2). IR (ATR) 2925, 1360, 1154, 560 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 4.68 (dd, *J* = 2.4, 11.0 Hz, 1H), 4.17-4.13 (m, 1H), 3.93 (ddd, *J* = 4.2, 10.4, 12.6 Hz, 1H), 3.29 (dd, *J* = 2.3, 11.3 Hz, 1H), 3.20-3.11 (m, 2H), 2.95 (dd, *J* = 11.1, 12.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 127.7, 127.5, 125.2, 76.1, 64.7, 49.2, 42.8. HRMS (ESI) *m/z* calcd for $C_{10}H_{14}NO$ $(M+H)^+$: 164.1075, found: 164.1083.

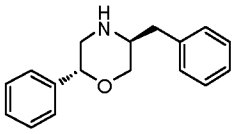
(2*R*,5*S*)-5-Methyl-2-phenylmorpholine (55)



Prepared as described above starting from morpholine **47** (29 mg, 0.088 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.96:0.04) afforded **55** (14 mg, 92% yield) as a colorless oil. R_f 0.65 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ −7.9 (*c* 0.75, CH_2Cl_2). IR (ATR) 3434, 2920, 2353, 1453, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400

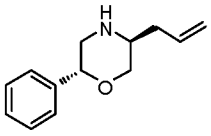
MHz): δ 7.36-7.32 (m, 5H), 5.98 (br s, 1H), 5.00 (dd, *J* = 2.2, 11.1 Hz, 1H), 4.10 (dd, *J* = 3.6, 12.6 Hz, 1H), 3.90 (dd, *J* = 11.0, 12.4 Hz, 1H), 3.58-3.50 (m, 1H), 3.46 (dd, *J* = 2.2, 12.7 Hz, 1H), 3.00 (dd *J* = 11.2, 12.7 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.2, 128.6, 126.0, 75.2, 70.4, 51.0, 49.4, 14.8. HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO$ $(M+H)^+$: 178.1232, found: 178.1232.

(2*R*,5*S*)-5-Benzyl-2-phenylmorpholine (56)



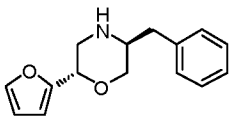
Prepared as described above starting from morpholine **48** (29 mg, 0.071 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **56** (15 mg, 83% yield) as a colorless oil. R_f 0.56 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –38.8 (*c* 0.75, CH_2Cl_2). IR (ATR) 2936, 2833, 2353, 1100, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.23 (m, 10H), 4.51 (dd, *J* = 2.5, 10.4 Hz, 1H), 4.04 (dd, *J* = 3.1, 11.2 Hz, 1H), 3.52 (dd, *J* = 10.4, 11.1 Hz, 1H), 3.16-3.10 (m, 1H), 3.07 (dd, *J* = 2.5, 12.1 Hz, 1H), 2.78-2.72 (m, 2H), 2.56 (dd, *J* = 8.8, 13.4 Hz, 1H), 2.27 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.0, 137.6, 129.1, 128.6, 128.3, 127.7, 126.6, 126.0, 78.7, 72.6, 55.6, 53.2, 38.6. HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO$ $(M+H)^+$: 254.1545, found: 254.1537.

(2*R*,5*S*)-5-Allyl-2-phenylmorpholine (57)



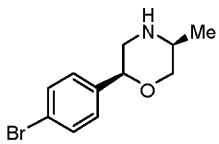
Prepared as described above starting from morpholine **49** (45 mg, 0.13 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **57** (13 mg, 86% yield) as a colorless oil. R_f 0.51 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –17.2 (*c* 0.65, CH_2Cl_2). IR (ATR) 3321, 3062, 2842, 2350, 1099 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 5H), 5.84-5.74 (m, 1H), 5.18-5.12 (m, 2H), 4.45 (dd, *J* = 2.5, 10.4 Hz, 1H), 4.00 (dd, *J* = 3.1, 11.1 Hz, 1H), 3.40 (dd, *J* = 10.7, 10.7 Hz, 1H), 3.11 (dd, *J* = 2.5, 12.1 Hz, 1H), 2.96-2.89 (m, 1H), 2.83 (dd, 10.5, 12.0 Hz, 1H), 2.21-2.15 (m, 1H), 2.07-2.00 (m, 1H), 1.85 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.2, 134.1, 128.3, 127.7, 126.0, 118.0, 78.9, 72.8, 53.4, 53.4, 36.8. HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ $(M+H)^+$: 204.1388, found: 204.1394.

(2*S*,5*S*)-5-Benzyl-2-(2-furyl)morpholine (58)



Prepared as described above starting from morpholine **50** (19 mg, 0.048 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **58** (9.5 mg, 82% yield) as a colorless oil. R_f 0.47 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ –50.3 (*c* 0.31, CH_2Cl_2). IR (ATR) 2929, 2850, 738, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.42 (m, 1H), 7.33-7.21 (m, 5H), 6.42-6.41 (m, 1H), 6.39-6.38 (m, 1H), 4.68 (dd, *J* = 3.6, 6.3 Hz, 1H), 3.79 (dd, *J* = 3.0, 11.4 Hz, 1H), 3.66 (dd, *J* = 5.2, 11.3 Hz, 1H), 3.39 (dd, *J* = 6.4, 12.5 Hz, 1H), 3.11-3.04 (m, 2H), 2.92 (dd, *J* = 8.3, 13.4 Hz, 1H), 2.80 (dd, *J* = 6.3, 13.6 Hz, 1H), 1.81 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.0, 142.1, 138.5, 129.1, 128.6, 126.4, 110.1, 107.9, 70.3, 68.5, 54.4, 45.0, 37.2. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NO_2$ $(M+H)^+$: 244.1338, found: 244.1329.

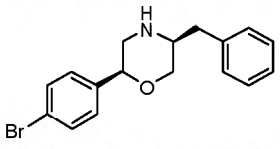
(2*S*,5*S*)-2-(4-Bromophenyl)-5-methylmorpholine (59)



Prepared as described above starting from morpholine **51** (80 mg, 0.195 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.9:0.1) afforded **59** (25 mg, 50% yield) as a colorless oil. R_f 0.12 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ +13.4 (*c* 0.18, CH_2Cl_2). IR (ATR) 3425, 2926, 2852, 2357, 1490, 1010 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.53-7.50 (m, 2H), 7.33-7.30 (m, 2H), 4.55 (dd, *J* = 3.1, 10.2 Hz, 1H), 3.93 (dd, *J* = 2.9, 12.1 Hz, 1H), 3.82 (dd, *J* = 1.3, 12.1 Hz, 1H), 3.26-3.22 (m, 1H), 3.10 (dd, *J* = 10.3, 13.2 Hz, 1H), 2.99 (dd, *J* = 3.0, 13.2 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (CD_3OD, 75 MHz): δ 139.7,

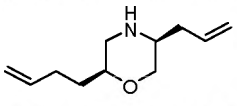
132.7, 129.1, 122.9, 77.9, 71.1, 48.0, 45.6, 15.0. HRMS (ESI) *m/z* calcd for $C_{11}H_{14}BrNO$ $(M+H)^+$: 256.0337, found: 256.0324.

(2*S*,5*S*)-5-Benzyl-2-(4-bromophenyl)morpholine (60)



Prepared as described above starting from morpholine **52** (39 mg, 0.081 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **60** (15 mg, 56% yield) as a colorless oil. R_f 0.58 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ +39.4 (*c* 0.33, CH_2Cl_2). IR (ATR) 3019, 2902, 2846, 2353, 1451, 741, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.20 (m, 9H), 4.53 (dd, *J* = 2.9, 10.3 Hz, 1H), 3.81 (m, 2H), 3.20 (dd, *J* = 10.6, 15.0 Hz, 1H), 3.13 (dd, *J* = 10.3, 12.8 Hz, 1H), 3.05-2.99 (m, 2H), 2.82 (dd, *J* = 3.0, 12.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.7, 140.4, 130.4, 129.7, 129.4, 128.9, 127.4, 127.2, 79.9, 69.4, 54.2, 47.6, 36.7. HRMS (ESI) *m/z* calcd for C17H19BrNO $(M+H)^+$: 332.0646, found: 332.0639.

(2*S*,5*S*)-5-Allyl-2-(but-3-enyl)morpholine (61)



Prepared as described above starting from morpholine **53** (26 mg, 0.08 mmol). Column chromatography (CH_2Cl_2/MeOH, 0.99:0.01→0.90:0.10) afforded **61** (12 mg, 86% yield) as a colorless oil. R_f 0.26 (CH_2Cl_2/MeOH, 0.9:0.1). $[\alpha]_D^{20}$ −15.4 (*c* 0.10, CH_2Cl_2). IR (ATR) 3417, 2926, 2866, 1645, 1446, 1111, 913 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.88-5.76 (m, 2H), 5.16-5.08 (m, 2H), 5.02 (ddd, *J* = 1.6, 3.7, 17.2 Hz, 1H), 4.97-4.93 (m, 1H), 3.66 (dd, *J* =2.9, 2.9 Hz, 2H), 3.48 (ddt, *J* = 3.2, 4.8, 8.2 Hz, 1H), 2.73 (dd, *J* = 8.8, 12.5 Hz, 1H), 2.70 (dd, *J* = 2.9, 10.1 Hz, 1H), 2.65 (dd, *J* = 3.2, 12.6 Hz, 1H), 2.47-2.34 (m, 2H), 2.22-2.04 (m, 2H), 1.70-1.59 (m, 2H), 1.48 (dddd, *J* = 4.9, 6.8, 9.3, 14.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 136.6, 117.9, 115.2, 76.4, 69.1, 52.8, 46.2, 35.4, 33.0, 30.8, HRMS (ESI) *m/z* calcd for $C_{11}H_{20}NO$ $(M+H)^+$: 182.1545, found: 182.1535.

5.10 References and notes

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Summary

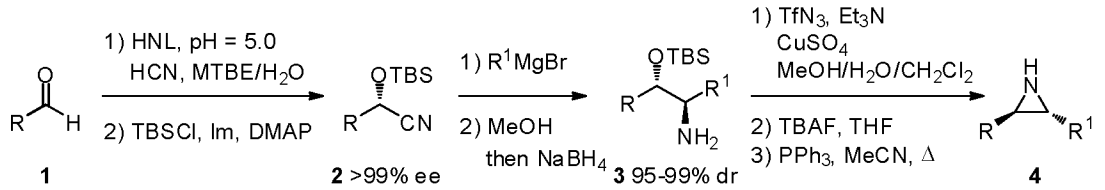
Nitrogen heterocycles form the basis of many pharmaceuticals and physiologically active natural products. Despite an abundance of methods to synthesize a large variety of different heterocycles, the relevance of these molecules drives a continuous interest in developing new synthetic pathways, preferentially with complete control over the relative and absolute configuration.

Over the years, non-racemic cyanohydrins have been recognized as versatile starting materials for various (bio)synthetic purposes. Not only because they are cheap and readily available chiral building blocks, but mainly because of their multifunctional character, offering a wide spectrum of opportunities for further structural modification. The existing methods for enantioselective cyanohydrin synthesis, more specifically through catalysis by metals, organic molecules and enzymes, have been extensively reviewed. Especially attractive is the application of hydroxynitrile lyases (HNLs) as catalysts for the enantioselective addition of HCN to prochiral aldehydes, since both (*R*)- and (*S*)-selective HNLs are readily available. Inspired by these unique opportunities, this thesis describes our research on the synthesis and application of enantiomerically pure cyanohydrins in constructing functionalized nitrogen heterocyclic compounds.

Chapter 1 provides an overview of the latest efforts of various groups concerning applications of non-racemic cyanohydrins in organic synthesis.

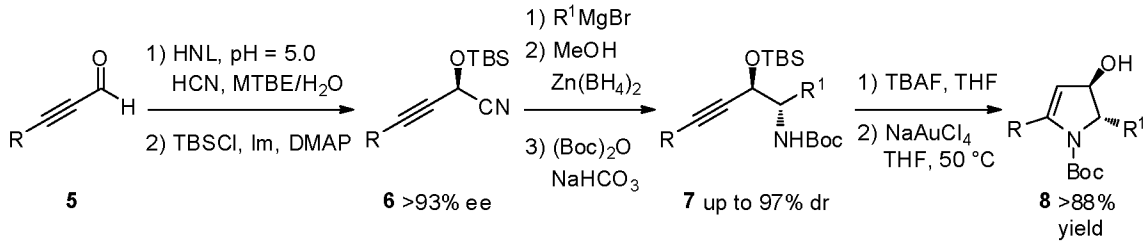
In Chapter 2, a newly developed chemoenzymatic approach to 2,3-disubstituted *trans*-aziridines **4** is detailed (Scheme 1). At the basis of this research, HNL-catalyzed cyanohydrin formation served to convert the functionalized aldehydes **1** into the corresponding cyanohydrins **2**. Upon treatment with different Grignard reagents the intermediate imines were formed, after which chelation-controlled diastereoselective reduction with $NaBH_4$ afforded the amino alcohols **3** in excellent optical purities and good yields. The amino alcohols **3** were then transformed *via* the corresponding azides into the targeted biologically relevant aziridine derivatives **4**.

Scheme 1 *Chemoenzymatic synthesis of trans-aziridines.*



Chapter 3 utilizes the reaction conditions for chemoenzymatic cyanohydrin formation described in Chapter 2 on acetylenic aldehydes **5** and subsequently deals with a novel approach toward 2,5-disubstituted-4-hydroxy-2-pyrrolines **8** (Scheme 2). Another key step involved a mild Au(III)-catalyzed 5-*endo*-dig cyclization of the diastereomerically enriched acetylenic amino alcohols **7**, obtained *via* Grignard addition onto the cyanohydrins **6** and $Zn(BH_4)_2$-mediated chelation-controlled diastereoselective reduction. Extensive investigation on the Au-catalyzed cycloisomerization finally led to the targeted pyrrolines **8** in optically pure form and without detectable pyrrole formation after column chromatography. Unfortunately, subsequent follow-up chemistry to synthetically elaborate the resulting pyrrolidines appeared to be surprisingly troublesome, mostly due to dehydration to the corresponding pyrrole analogues.

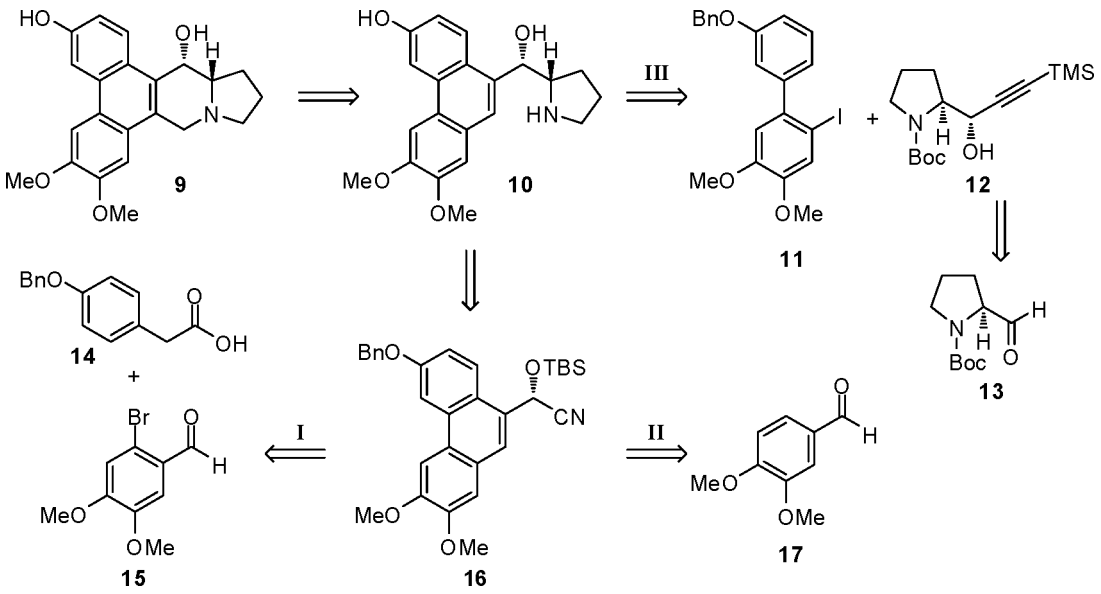
Scheme 2 *Chemoenzymatic synthesis of 4-hydroxy-2-pyrrolines.*



Stimulated by the results in the previous chapters, Chapter 4 highlights three attempts toward an asymmetric synthesis of the potent antitumor phenanthroindolizidine **9** (Scheme 3). Two of these approaches were thought to proceed through chemoselective HNL-mediated synthesis of the enantiopure phenanthrene-based cyanohydrin **16**. Synthesis of the precursors proceeded without difficulty, however, we have not been able to form the desired cyanohydrin products *via* asymmetric HNL-mediated hydrogen cyanide addition. The third route details an approach based on diastereocontrolled acetylide addition to Boc-(*S*)-prolinal **13** with which both the relative and absolute stereochemistry could be predictably installed. Despite

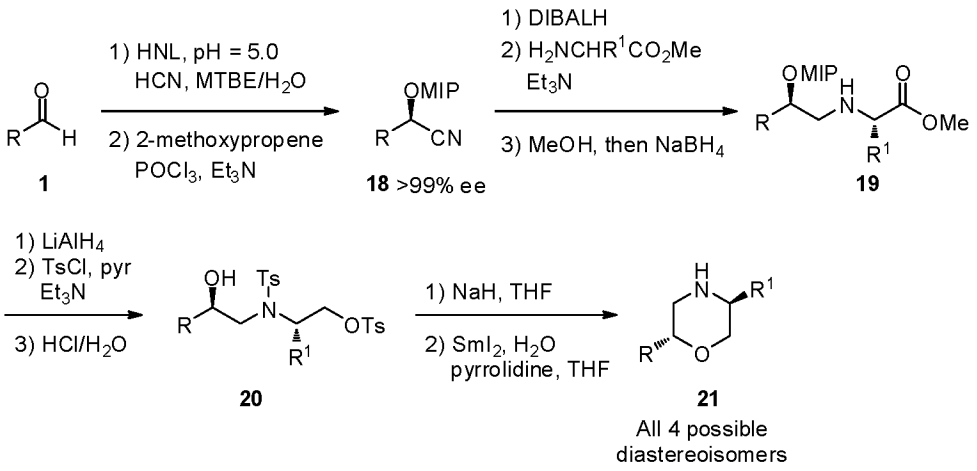
numerous attempts, ring closure of the biphenyl moiety to arrive at the phenanthrene scaffold **10** has remained unsuccessful.

Scheme 3 *Toward an asymmetric synthesis of the phenanthrene natural product* ***9****.*



Finally, Chapter 5 details the application of cyanohydrins **18** in the synthesis of *cis*- and *trans*-2,5-disubstituted morpholines **21** (Scheme 4). Starting from enantiomerically pure cyanohydrins **18**, subsequent formation of diastereomerically pure amino esters **19** *via* a three-step one-pot reduction–transimination–reduction sequence, followed by ester reduction and simultaneous protection, provided the cyclization precursors **20**. Ring closure under basic conditions to arrive at the morpholine skeleton and SmI_2-mediated reductive detosylation delivered a third set of potentially biologically relevant nitrogen-containing heterocyclic target structures **21**.

Scheme 4 *Chemoenzymatic synthesis of cis- and trans-2,5-disubstituted morpholines* ***21***.



Samenvatting

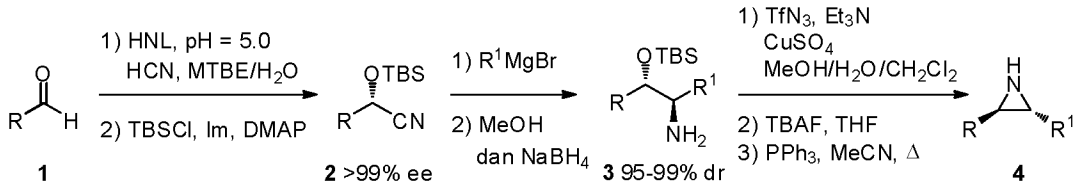
Stikstof-bevattende ringsystemen vormen de basis voor veel farmaceutische verbindingen en fysiologisch actieve natuurstoffen. Ondanks dat er verschillende methoden bestaan om een grote diversiteit van deze heterocyclische systemen te maken, leidt de relevantie van deze moleculen tot het continu ontwikkelen van nieuwe syntheseroutes, bij voorkeur met volledige controle over zowel de relatieve als absolute configuratie.

Reeds door de jaren heen worden cyaanhydrinen gezien als veelzijdige bouwstenen voor verschillende (bio)synthetische doeleinden. Dit komt niet zozeer doordat ze goedkoop en eenvoudig toegankelijk zijn, maar hoofdzakelijk door hun multifunctionele karakter. De aanwezigheid van diverse functionele groepen maakt deze bouwstenen aantrekkelijk voor verdere structuurmodificatie. Verschillende katalytische methoden voor de synthese van enantiomeerzuivere cyaanhydrinen, gebruikmakend van metalen, organische moleculen of enzymen, zijn beschreven in de literatuur. Doordat zowel (*R*)- als (*S*)-selectieve hydroxynitrillyasen (HNLs) gemakkelijk te verkrijgen zijn, is de toepassing van deze HNLs als katalysatoren voor de enantioselectieve additie van HCN aan prochirale aldehyden een aantrekkelijke manier om cyaanhydrinen te synthetiseren. Geïnspireerd door deze unieke eigenschappen wordt in dit proefschrift het onderzoek naar de synthese en toepassingen van enantiomeerzuivere cyaanhydrinen als bouwstenen voor de ontwikkeling van gefunctionaliseerde stikstof-bevattende ringsystemen beschreven.

Hoofdstuk 1 biedt een overzicht van uiteenlopende toepassingen van niet-racemische cyaanhydrinen in de organische synthese die in de afgelopen jaren in de literatuur zijn verschenen.

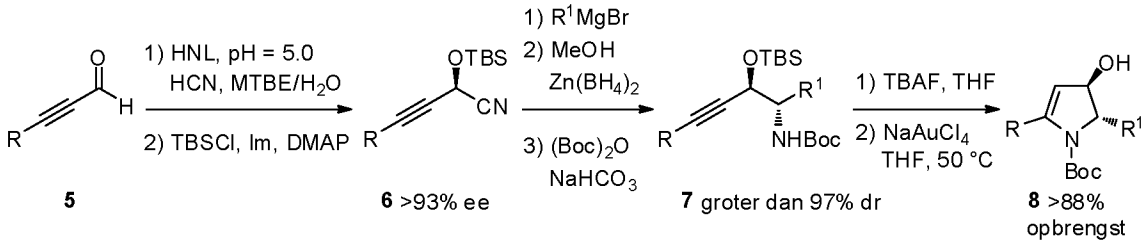
In Hoofdstuk 2 wordt een nieuw ontwikkelde chemoenzymatische benadering voor de synthese van 2,3-digesubstitueerde *trans*-aziridinen **4** behandeld (Schema 1). De basis hiervan is een HNL-gekatalyseerde omzetting van aldehyden **1** naar de overeenkomstige cyaanhydrinen **2**. Middels een reactie met verschillende Grignardreagentia werden de instantaan gevormde imines onderworpen aan een chelatie-gecontrolleerde diastereoselectieve reductie met $NaBH_4$ wat leidde tot vorming van aminoalcoholen **3** in uitstekende optische zuiverheid en hoge opbrengsten. De aminoalcoholen **3** werden hierna via het overeenkomstige azide omgezet in de gewenste biologisch actieve aziridine analoga **4**.

Schema 1 *Chemoenzymatische synthese van trans-aziridinen.*



In Hoofdstuk 3 worden de reactiecondities voor de chemoenzymatische cyaanhydrinvorming toegepast op de acetyleenbevattende aldehyden **5**, reeds beschreven in Hoofdstuk 2, en wordt vervolgens een nieuwe route naar 2,5-digesubstitueerde 4-hydroxy-2-pyrrolinen **8** beschreven (Schema 2). Een andere sleutelstap omvat een milde Au(III)-gekatalyseerde 5-*endo*-dig ringsluiting van diastereomeer-verrijkte acetyleen-bevattende aminoalcoholen **7**. Deze laatste verbindingen zijn verkregen door een Grignardadditie uit te voeren op de cyaanhydrinen **6** en vervolgens een $Zn(BH_4)_2$-gekatalyseerde chelatie-gecontroleerde diastereoselectieve reductie uit te voeren. Uitgebreid onderzoek naar de Au-gekatalyseerde cycloisomerisatie leidde uiteindelijk tot de gewenste pyrrolinen **8** in optisch zuivere vorm en zonder detecteerbare pyrroolvorming na kolomchromatografie. Helaas bleek de vervolgchemie om de desbetreffende pyrrolidinen te verkrijgen moeilijk. Dit werd voornamelijk veroorzaakt door dehydratatie naar de overeenkomstige pyrroolderivaten.

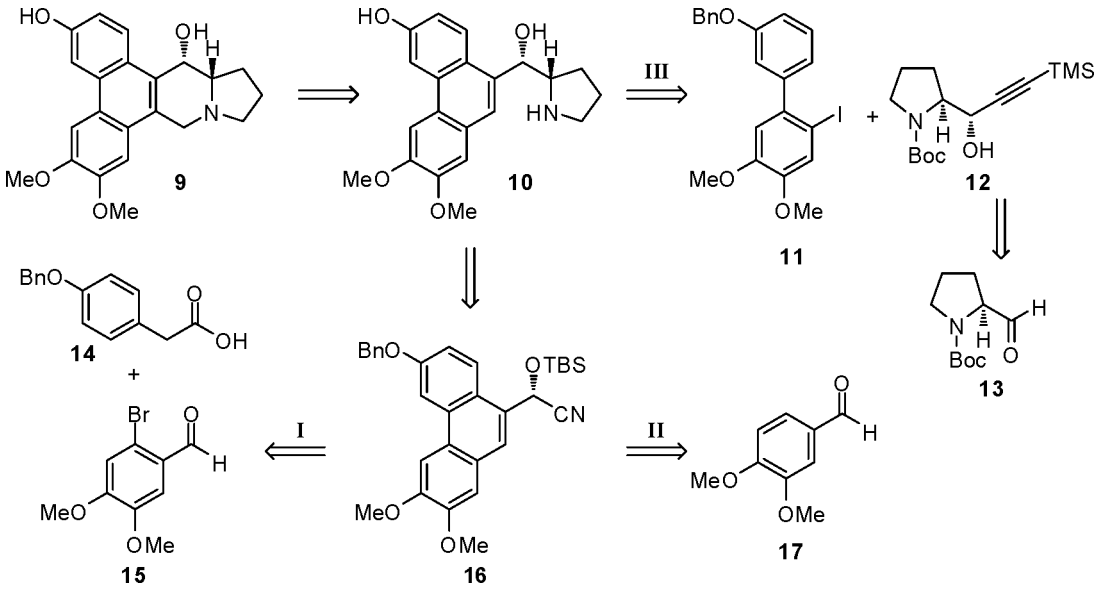
Schema 2 *Chemoenzymatische synthese van 4-hydroxy-2-pyrrolinen.*



Gestimuleerd door de resultaten verkregen in de voorafgaande hoofdstukken, belicht Hoofdstuk 4 drie pogingen naar een asymmetrische synthese van de potentiële antikanker verbinding phenanthroindolizidine **9** (Schema 3). Twee van deze routes waren aanvankelijk gebaseerd op een chemoselectieve HNL-gekatalyseerde synthese van enantiomeerzuiver phenanthreencyaanhydrin **16**. De synthese van de bouwstenen verliep probleemloos, echter waren we niet in staat om de gewenste cyaanhydrinen te maken via de asymmetrische HNL-gekatalyseerde waterstofcyanide additiereactie. De derde route beschrijft een ontwikkeling die

gebaseerd is op een diastereogecontroleerde acetylide additie aan Boc-(*S*)-prolinal **13**, waarbij zowel de relatieve als absolute stereochemie voorspelbaar kon worden ingebouwd. Ondanks uiteenlopende pogingen is het echter niet gelukt om een ringsluiting uit te voeren op de biphenylstructuur die zou moeten leiden tot het phenanthreenskelet **10**.

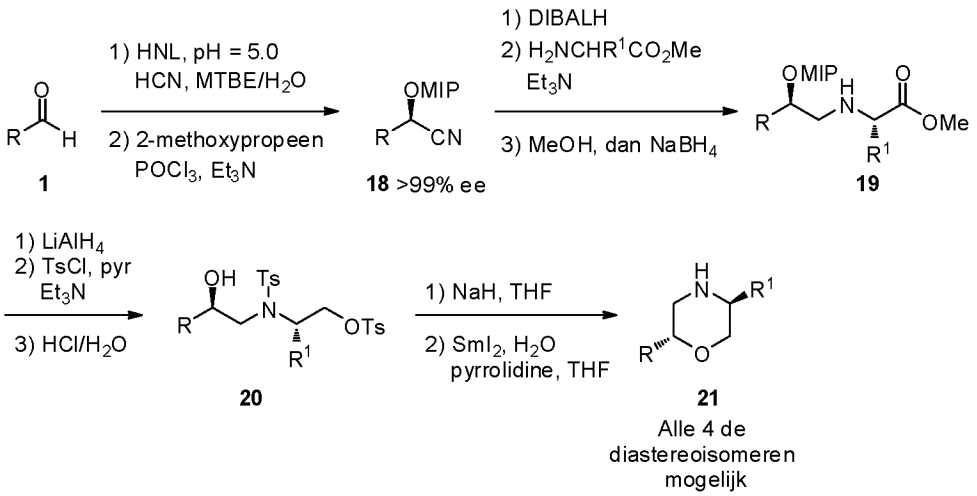
Schema 3 *Naar een asymmetrische synthese van phenanthreen natuurproduct* ***9****.*



Tenslotte beschrijft Hoofdstuk 5 de toepassing van cyaanhydrinen **18** in de synthese van *cis*- en *trans*-2,5-digesubstitueerde morfolinen **21** (Schema 4). Uitgaande van enantiomeerzuivere cyaanhydrinen **18**, werden door middel van een gecombineerde driestapsreactie bestaande uit een reductie–transiminering–reductie, de aminoalcoholen **19** verkregen. Vervolgens werden deze structuren omgezet via reductie van de ester en een simultane beschermingsstap waarna de precursors **20** werden verkregen.

Een derde set van mogelijk biologisch relevante stikstof-bevattende heterocyclische doelstructuren **21** werd gerealiseerd door een ringsluiting onder basische condities uit te voeren om te komen tot het morfolineskelet, gevolgd door een SmI_2-gekatalyseerde reductieve detosylering.

Schema 4 *Chemoenzymatische synthese van cis- en trans-2,5-digesubstitueerde morfolinen* ***21****.*



Dankwoord

Na vele uren aan de labtop te hebben doorgebracht, meestal onder consumptie van de nodige "tassen" koffie, en met zo nu en dan wat gefoeter en gevloek (##@$%$##) omdat de labtop ineens een ander leven gaat leiden en dat "ding" niet wilt doen wat jij wilt dat gebeurt, rest mij eigenlijk nog maar één ding: het schrijven van het dankwoord. Teruggaand naar het begin van mijn AiO-periode lijken die vier jaar ruimschoots voldoende om je promotieonderzoek af te ronden. Echter na anderhalf jaar hard werken begin je je toch af te vragen of dit alles is wat je tot nu toe hebt gepresteerd en dan lijkt het idee om uiteindelijk zo'n boekje in elkaar te moeten draaien bijna godsonmogelijk. En dan, zoals "Herr Kaiser" al vermeldde in zijn dankwoord in ik quote: "bekruipt je het gevoel dat de resterende tijd omgekeerd evenredig is met de hoeveelheid werk die nog moet worden verzet". Wat mij betreft klopt dat wel degelijk! Gelukkig ontstaat er eindelijk (wel langzaam) een "ent", of lijkt er "een vaag lijntje" aan de horizon op te doemen en voordat je het in de gaten hebt, is er solid ground. Uiteindelijk groeit dit alles uit tot de rode draad van het proefschrift. Gaandeweg worden het steeds meer lijntjes waarvan er steeds meer tot een succes gaan leiden Wat uiteindelijk tot "best een aardig geheel" heeft geleid. Tijdens het schrijven van het proefschrift blijkt dan toch eens te meer dat je net iets meer te vertellen hebt dan aanvankelijk gedacht. Bij het doorspitten van de labjournaals passeren veel leuke momenten en situaties de revue die ik zowel op als buiten het lab heb meegemaakt en die ervoor gezorgd hebben dat ik de afgelopen vier jaar met veel plezier AiO ben geweest. Eén ding weet ik nu zeker: ik heb er zeker geen spijt van gehad. Ik wil dit dankwoord dan ook graag gebruiken om iedereen die hieraan een bijdrage heeft geleverd te bedanken.

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Uiteraard kon al dat werk, beschreven in dit proefschrift nooit door mij alleen verzet worden. Tijdens mijn promotie heb ik het genoegen gehad om verschillende studenten te

mogen begeleiden (Niek, Matthijs, Elena, Steven, Jody, Laurens, Marleen, Ezra, Gaston). Een bedankje is hier zeker wel op zijn plaats! Allereerst wil ik Niek Vermue bedanken voor zijn bijdrage aan hoofdstuk 2. Niek jij hebt tijdens je ministage de basis gelegd die ertoe geleid heeft dat we na heel wat plezierig experimenteren en klooien in het lab uiteindelijk toch een route vonden naar de aziridines. Je verslag heeft een *tijdje* op zich laten wachten (al met al zo'n anderhalf jaar), vermoedelijk stond je al die tijd druk friet te bakken in Zeeland....? Toch wil ik je bedanken voor je bijdrage en je veel succes wensen met je studie, want ik neem aan dat deze nog steeds "in de steigers staat"??!

Matthijs (aka Blondy), tot twee maal toe de snelste op de kartbaan, was jij mijn eerste hoofdvakstudent en heb je een enorme bijdrage geleverd aan mijn onderzoek. Je kwam precies op het juiste moment om je tanden te zetten in de chemie die ik samen met Niek was begonnen en om deze verder in goede banen te leiden. Maar hard werken wordt beloond en we hebben dit alles mooi kunnen verpakken in een JOC publicatie. Ik wens je dan ook heel veel succes en vooral ook veel plezier tijdens je promotieonderzoek. P.S.: geen pot met rhodamine meer laten vallen he, dat geeft zo'n rommel!

During the summer of 2008 Elena Duran Verdasco visited our laboratory in Nijmegen as an Erasmus student. Elena, I can still remember you as a shy Spanish girl the first time we met. But along the way, I think you learned a lot, not only about the ups and downs of research (on morpholines), but also of the great student life in Nijmegen. I really enjoyed having you in our lab and I wish you all the best with your job in Spain.

Steven (aka Stefanie ofwel "the cornerman"), jij zette het onderzoek aan morfolines voort en ook al zat de chemie zo nu en dan tegen, je was nooit snel tevreden en gaf niet op. Je kwam er o.a. achter dat de in de literatuur beschreven experimenten niet altijd te reproduceren waren en het leek erop dat ook de uitvoering hiervan op papier toch allemaal iets simpeler leek dan dat het daadwerkelijk was. Uiteindelijk heb je toch doorgezet wat resulteerde in een mooie publicatie in de JOC. Veel succes met je promotieonderzoek in Schotland.

Laurens tijdens je korte stage, heb je een enorme werklust getoond en vormde ook jouw werk een basis voor succes. Gaston, als HLO'er was jij mijn aller-allerlaatste student die ik mocht begeleiden. Jij bent verder gegaan met het werk van Laurens en je geweldige gedrevenheid, creativiteit en vastberadenheid hebben ertoe geleid dat je tijdens je afstudeerstage een indrukwekkende hoeveelheid verbindingen hebt gemaakt. Jullie werk samen heeft nog een mooie publicatie opgeleverd en fantastisch dat je aan het eind ook nog "even" de gouden spatel hebt weten binnen te tikken. Veel succes met jullie studies!

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Bas

List of publications

Publications

- B. Ritzen; F. L. van Delft; F. P. J. T. Rutjes: "*Synthetic Applications of Enantiopure Cyanohydrins" manuscript in preparation.*

- B. Ritzen; G. J. J. Richelle; L. Brocken; F. L. van Delft; F. P. J. T. Rutjes: "*Enantioselective Chemoenzymatic Synthesis of 4-Hydroxy-2-Pyrrolines*" *manuscript in preparation.*

- B. Ritzen; S. Hoekman; E. Durán Verdasco; F. L. van Delft; F. P. J. T. Rutjes: "*Enantioselective Chemoenzymatic Synthesis of cis- and trans-2,5-Disubstituted Morpholines*" *J. Org. Chem.* **2010**, *75*, 3461-3464.

- B. Ritzen; M. C. M. van Oers; F. L. van Delft; F. P. J. T. Rutjes: "*Enantioselective Chemoenzymatic Synthesis of trans-Aziridines*" *J. Org. Chem.* **2009**, *74*, 7548-7551.

- H. H. W. Thijssen; B. Ritzen: "*Acenocoumarol Pharmacokinetics in Relation to Cytochrome P450 2C9 Genotype*" *Clin. Pharmacol. Ther.* **2003**, *74*, 61-68.

Patents

- P. L. J. M. Zeeuwen; P. A. M. Jansen; J. Schalkwijk; F. P. J. T. Rutjes; B. Ritzen: "*Pantothenic Acid Derivatives and Their Use in the Treatment of Microbial Infections*" Patent application filed.

- P. J. L. M. Quaedflieg; B. J. M. Plum; B. Ritzen; A. J. A. A. Dias; C. Cusan; C. H. M. Schepers: "*Enzymatic Conjugation of Bioactive Moieties*" PCT Int. Appl. **2009**, WO 2009101178 A1.

- P. J. L. M. Quaedflieg; C. Cusan; B. Ritzen; A. J. A. A. Dias: "*Process for Selective Enzymatic Hydrolysis of Pendant Esters of a Polymer*" PCT Int. Appl. **2008**, WO 2008155381 A1.

Curriculum Vitae

Bas Ritzen was born on the 20th of June 1982 in Heerlen, the Netherlands. He attended Bernardinus College secondary school, which he finished in 1999. He then started a Bachelor study in chemistry at the Zuyd University of Applied Sciences where he received his BA.Sc. title in 2003 (organic chemistry). Afterwards he started his Master in Chemistry at Radboud University Nijmegen, where he obtained his M.Sc. degree in 2005, graduating *cum laude*. He performed his master internship under the supervision of Prof. dr. F.P.J.T. Rutjes and Dr. F.L. van Delft. The project involved the synthesis of 4,6-linked peptide-based 2-deoxystreptamine derivatives that – upon incorporation into aminoglycoside structures – may improve the binding to RNA and hence act as antibiotic compounds.

Before the start of his PhD in mid 2006, an additional industrial traineeship was performed to expand his knowledge towards the industrial aspects of organic chemistry. During this five months period, chemical and enzymatic technologies with regard to peptide synthesis were developed. The last three months he was recruited as a temporary employee at the aforementioned department.

In September 2006, he started his PhD under the supervision of Prof. dr. F.P.J.T. Rutjes in the synthetic organic chemistry group of the Institute for Molecules and Materials at Radboud University Nijmegen. The aim of the research was to develop novel synthetic methodologies for the synthesis of various nitrogen heterocycles using enantiopure cyanohydrins as strategic synthons and application of the newly developed methodology in natural product synthesis. The results thereof are described in this thesis.

Moreover, in a project in collaboration with Prof. dr. J. Schalkwijk (dermatology group, Radboud University Nijmegen Medical Center), novel analogues of pantetheine were synthesized, which were evaluated as inhibitors of pantetheinase activity.

After a short stay at the spin-off company Synaffix, he is currently working as a post-doctoral fellow within the DSM R&D department (Geleen, The Netherlands).